RAPID RISK ASSESSMENT

Candida auris in healthcare settings – Europe

First update, 23 April 2018

Main conclusions and options for response

Candida auris poses a risk for patients in healthcare facilities across Europe due to its propensity to cause outbreaks and its antifungal resistance. Difficulties with laboratory identification and lack of awareness of this *Candida* species may delay early detection increasing the potential for horizontal transmission. *C. auris* was first identified in 2009 and within a few years has emerged as a cause of healthcare-associated infections. Outbreaks have been reported in countries in five continents. The number of reported *C. auris* cases in European countries has increased significantly since the last ECDC rapid risk assessment on *C. auris* in December 2016. There continues to be a need to raise awareness of *C. auris* in European healthcare facilities, so that they may adapt their laboratory testing strategies and implement enhanced infection prevention and control measures where necessary.

Options to reduce identified risks: prevention of transmission of *C. auris* in healthcare settings

Laboratory detection of *C. auris*

Recognition of *C. auris* requires that isolates of *Candida* species from invasive infections are accurately identified to the species level. A correct identification of *C. auris* is possible using either Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, provided that *C. auris* is included in the reference profile database, or DNA sequencing of specific domains of the ribosomal genes. When these tests are not available at clinical laboratory level, referral of non-*albicans Candida* spp. invasive isolates to a reference mycology laboratory is advisable, especially if identified by biochemical tests as *Candida haemulonii, Candida famata, Candida sake, Rhodotorula* species *or Saccharomyces* species. This is particularly important for hospitals with an increased incidence of infection by non-*albicans Candida* species or those that admit patients transferred from a facility reporting a *C. auris* outbreak. Where *Candida* species isolates are tested for antifungal susceptibility, resistance to fluconazole is another characteristic that should prompt tests to speciate the *Candida* isolate.

Standard infection control measures

Good standard infection control, including environmental cleaning, adequate cleaning and reprocessing of medical devices, and adequate capacity of microbiological laboratories, as well as sufficient capacity of healthcare facilities for patient isolation, are the basis for the prevention of transmission of any pathogen in healthcare settings.

Suggested citation: European Centre for Disease Prevention and Control. *Candida auris* in healthcare settings – Europe – first update, 23 April 2018. Stockholm: ECDC; 2018.

Preventing transmission from patients known to carry C. auris

Early, robust action is recommended to prevent an outbreak as these can be prolonged, costly and may pose significant risk to compromised patients. Prompt notification of *C. auris* to the clinical and infection control teams is essential to implement infection control precautions in a timely manner and to ensure vigilance for development of infections in patients found to be colonised. The detection of a case of *C. auris* should trigger an investigation including a detailed case review and screening of close contact patients for *C. auris* carriage. More extensive contact tracing can be considered based on a case-by-case risk assessment (for example, taking into account the type of patient population and ward in which the *C. auris* case is detected, and the extent of *C. auris* colonisation and of the contacts of the affected patient).

Infection control options for hospitals to consider implementing include enhanced control measures such as contact precautions, single room isolation or patient cohorting, and dedicated nursing staff for patients who are colonised or infected with *C. auris.* As there are currently no established protocols for decolonisation and determining when it is safe to end isolation, these precautions need to be applied until the discharge of the patient from the hospital. Screening of close contacts of identified cases for *C. auris* carriage with axilla and groin swabs is an important component of the response to *C. auris*. Other sites (urine, wounds, catheter exit sites, throat etc.) can be sampled, if clinically relevant or indicated.

Emphasis is required on the terminal cleaning and disinfection of rooms after discharge of patients who carry, or are infected with, *C. auris*, using chlorine-based disinfectants (at a concentration of 1 000 ppm), hydrogen-peroxide or other disinfectants with documented fungicidal activity. Quaternary ammonium compound disinfectants should be avoided. Single use equipment or equipment specific to a *C. auris* patient or cohort is preferable where possible as patient shared equipment has been found to be contaminated with *C. auris* in an outbreak situation . Ensuring that cleaning and disinfection of reusable equipment (e.g. monitoring devices, thermometers, pulse oximeters, blood pressure measuring instruments, etc.) is performed according to manufacturer's instructions is also important. Environmental sampling or screening of healthcare workers are not routinely recommended.

Additional control options for outbreaks

Raising awareness and providing education to all healthcare groups is essential to manage the outbreak. Prompt initiation of an epidemiological investigation, complemented by cross-sectional screening of patients for *C. auris* carriage, is useful to establish the source of the outbreak and thus prevent further cases. Potentially effective enhanced measures to control *C. auris* outbreaks include regular active surveillance cultures for *C. auris* carriage of all patients in affected wards, cohorting of *C. auris*-positive patients with dedicated nursing staff in separate areas, as well as rigorous environmental cleaning and disinfection. Education and practice audits to improve compliance of healthcare workers with hand hygiene, contact precautions and supervision of appropriate implementation of environmental cleaning are important supportive interventions. Hospital senior management support is needed to provide adequate resources for the implementation of appropriate infection control measures.

Antimicrobial stewardship

Although there is no evidence for a specific beneficial effect of antimicrobial stewardship on the emergence and spread of *C. auris*, it is likely that an environment with a high level of broad-spectrum antibacterial and antifungal use will favour the emergence of multidrug-resistant yeasts, such as *C. auris*. Therefore, the implementation of antimicrobial stewardship is likely to mitigate the risks of *C. auris* acquisition and transmission, as well as being an essential component of strategies to reduce antimicrobial resistance in general. The need for antifungal prophylaxis should be reviewed in terms of risk-benefit analysis in settings with evidence of *C. auris* transmission.

Prevention of inter-hospital transmission, including cross-border transmission

Admission screening for *C. auris* carriage and pre-emptive isolation of patients who are transferred from, or have recently been admitted to hospitals that have detected *C. auris* cases should be considered. This implies that affected facilities need to notify the receiving healthcare facilities and clinicians in the case of transfer of patients with *C. auris* carriage or infection. Moreover, gathering reliable epidemiological data through notification of *C. auris* cases to public health authorities and exchange of information through electronic early warning platforms, such as the Epidemic Intelligence System (EPIS), will enable informed and coordinated risk management actions by public health authorities across the EU/EEA.

Improvement of preparedness in EU/EEA countries

EU/EEA countries should consider alerting clinicians and microbiologists in their healthcare facilities and associated clinical microbiology laboratories to raise awareness about this emerging fungal pathogen with epidemic potential, with the aim of adapting laboratory testing practice at primary and reference levels and establishing specific control measures in a timely manner. National guidelines for laboratory testing and control measures for *C. auris* will enable the implementation of appropriate measures in healthcare facilities. Sharing experiences of outbreaks and implementation of control measures can be facilitated by ECDC.

Improvement of laboratory capacity for detection and antifungal susceptibility testing of C. auris

As not all laboratories serving healthcare facilities have the capacity for *C. auris* identification and susceptibility testing of the whole panel of antifungal agents, a national mycology reference laboratory could assist clinical laboratories with *C. auris* identification, antifungal susceptibility testing, molecular typing, and epidemiological investigations. The reference laboratory may also issue guidance for local laboratories on how to proceed with difficult-to-identify *Candida* species isolates, and isolates suspected as being *C. auris*, and provide instructions for referring samples for further testing and for reporting results. Multi-country laboratory collaboration across the EU/EEA could be helpful to perform centralised reference antifungal susceptibility testing of invasive *C. auris* isolates and identify correlates of clinical treatment outcomes.

Case finding and improved surveillance for C. auris infections

EU/EEA countries may consider laboratory-based notification of *C. auris* invasive infections and prospective data collection at the national level, especially if cases and outbreaks have already occurred in the country. Surveillance systems for healthcare-associated infections should consider updating their definitions to include *C. auris* in the list of reportable pathogens associated with healthcare-associated infections.

Source and date of request

Request from the European Commission on 4 April 2018 to update the rapid risk assessment published on 19 December 2016.

Public health issue

Candida auris is an emerging fungal pathogen associated with outbreaks of invasive infection, including candidemia, in healthcare settings worldwide. In Europe, hospital outbreaks caused by *C. auris* have occurred in the UK and Spain. These hospital outbreaks have been difficult to control despite enhanced control measures.

C. auris can cause invasive infections in patients with severe underlying diseases or immunosuppression, and most *C. auris* isolates are resistant to fluconazole. Resistance to other antifungal agents has been reported, and multidrug-resistant *C. auris* isolates with resistance to all three main classes of antifungals have been described. Unlike other *Candida* species, *C. auris* seems to have a high propensity for patient-to-patient transmission in healthcare settings, possibly related to environmental contamination, or transient person or device colonisation. Commercially available laboratory tests used by clinical laboratories might fail to identify *C. auris*.

This rapid risk assessment update appraises the risk for spread of *C. auris* in hospitals in the European Union and European Economic Area (EU/EEA) countries, considering the newly available information from the ECDC survey on the epidemiological situation as well as laboratory capacity and preparedness for *C. auris* in EU/EEA countries.

Consulted experts

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Disease background information

Invasive candidiasis is the most common fungal disease in hospitalised patients [1]. In the *ECDC point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals 2011–2012*, *Candida* spp. was the fifth most common pathogen associated with bloodstream infections, isolated in 7.4% of all documented cases [2]. While *C. albicans* remains the predominant cause of invasive candidiasis, there has been a shift towards an increasing proportion of non-*albicans Candida* species such as *C. glabrata* in recent years [1,3].

Candida auris is a newly emerging yeast that was first described in 2009 after isolation from the ear canal of a Japanese patient [4], and has subsequently been associated with invasive infections and outbreaks in healthcare settings. *C. auris* cases have been reported from several countries in different continents such as South Korea [5], South Africa [6], India [7], Pakistan [8], Kuwait [9], Columbia [10], Venezuela [11], Israel [12], Oman [13], Kenya [14], the UK [15], Spain, Germany, France, Austria, Norway [16], Canada [17] and the USA [18]. A published laboratory-based study has also included isolates from Brazil [19].

C. auris infections include bloodstream infections, wound infections and ear infections [4,5,9,15]. The majority of the published cases have been *C. auris* bloodstream infections. *C. auris* has also been isolated from urine [18], though this may have represented carriage rather than infection.

Non-*albicans Candida* spp. have emerged in healthcare settings worldwide, presumably related to the use of prophylactic antifungal drugs in high-risk populations [20], but *C. auris* seems to be unique in its propensity to be transmitted between patients and cause outbreaks in healthcare settings. A number of hospital outbreaks have been reported and several molecular studies confirming intra- or interhospital transmission of *C. auris* have been published [7,11,15].

Laboratory identification, molecular typing and antimicrobial susceptibility testing

In the context of the emergence of *C. auris* and the increase of antifungal resistant *Candida* infections, isolates of *Candida* non-*albicans* from invasive infections should be identified to species level. *C. auris* cannot be identified based on microscopy or growth on chromogenic agars [21]. *C. auris* isolates are germ tube test negative and produce colonies that may appear pale purple, beige or pink on the CHROMagar Candida agar medium. *C. auris* is able to grow at 42°C. Biochemical testing can misidentify *C. auris* using Vitek-2, BD Phoenix, MicroScan instruments or API strips. Therefore, further testing needs to be undertaken if biochemical tests identify yeast isolates from blood cultures as *Candida haemulonii*, *Saccharomyces cerevisiae* or other commonly misidentified *Candida* species [6,21–24].

Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry can reliably differentiate *C. auris* from other *Candida* species as long as the *C. auris* spectrum is included in the reference database and care is given to an appropriate extraction method [23,25]. Alternatively, molecular identification of *C. auris* can be performed by sequencing various DNA loci within specific domains of ribosomal genes (18S rDNA, 28S rDNA or internal transcribed spacers ITS1, ITS2) [7,24]. A PCR assay for rapid identification of *C. auris* and closely related species has been developed, based on rDNA amplicon melting temperature analysis [26]. This assay and other rapid *Candida* detection assays in development await further clinical evaluation of diagnostic accuracy.

Molecular typing of *C. auris* can be performed using a variety of methods. Sequencing of rDNA loci (D1/D2 or ITS regions) can be used to differentiate between the four major phylo-geographic clades of this species. Further delineation of local hospital outbreaks require higher resolution methods, including typing by amplified fragment length polymorphism (AFLP) and whole genome sequencing analysis [24].

Minimum inhibitory concentration (MIC) clinical breakpoints for *C. auris* have not yet been established, therefore breakpoints of related *Candida* species have been used for the interpretation of antifungal susceptibility testing [8]. The EUCAST reference broth microdilution method can be used and interpreted with non-species-related clinical breakpoints for fluconazole susceptibility [27]. A comparison of the EUCAST and CLSI broth microdilution methods showed very similar MIC values and estimated epidemiological cut-off values for a range of antifungal agents against a collection of *C. auris* isolates from India, confirming uniform resistance to fluconazole [28].

Active surveillance cultures for *C. auris* among contact patients are an important part of outbreak control measures. In the 2015–2016 UK outbreak, contact patients were screened at the following sites: nose, axilla, groin, throat, rectum/faeces, vascular line and drain exit sites as well as from clinical samples such as urine, wound, drain fluid and respiratory specimens [15,24]. In the USA, patient colonisation screening cultures had the highest yield with combined axilla and groin swabs supplemented, as clinically indicated, by other samples such as swabbing at any indwelling catheter exit sites [29].

Antifungal resistance

Subject to use of various tentative breakpoints for susceptibility testing of outbreak related isolates, the vast majority of the *C. auris* isolates described worldwide have been resistant to fluconazole, and multidrug-resistant isolates have been demonstrated at variable rates to other azoles, to amphotericin B, and to echinocandins, depending on the study [8,28-30].

Event background information

Cases and outbreaks of *C. auris* in EU/EEA Member States

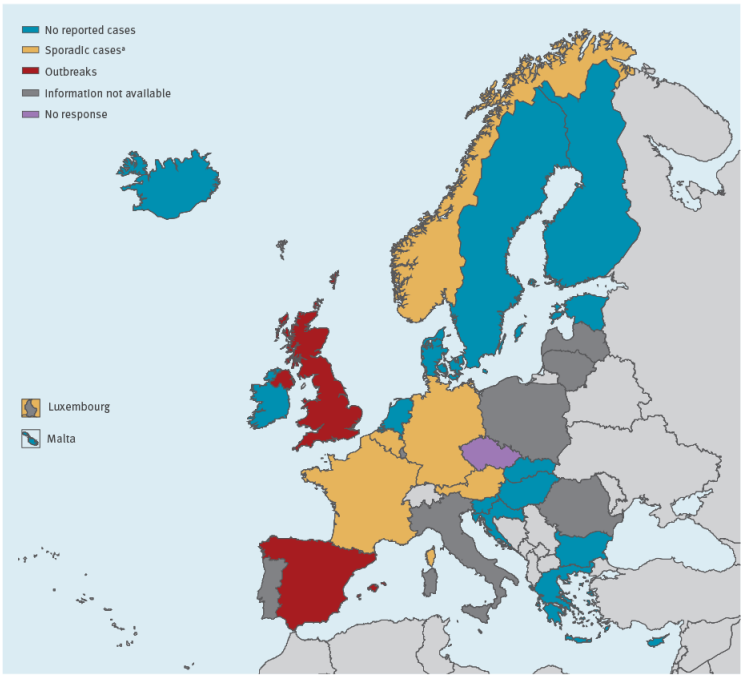
In response to the ECDC *C. auris* survey, 620 *C. auris* cases were reported from six EU/ EEA countries for the period 2013–2017. During this period, cases were reported from Spain (n = 388), the UK (n = 221), Germany (n = 7), France (n = 2), Belgium (n = 1) and Norway (n = 1) (Table 1, Figure 1) [16]. Austria detected one case in January 2018. The majority of cases were reported as colonisation (n = 466; 75.2%), while a bloodstream or other type of infection was reported in 150 (24.2%) cases. For four (0.6%) cases, the colonisation/infection status was unknown.

Table 1. Number of *Candida auris* cases detected in the EU/EEA, 2013–2017 (n = 620)[a] [16]

Year	*C. auris* bloodstream infection		Other type of *C. auris* infection		*C. auris* colonisation		Cases of unknown infection/colonisation status		Total
	n	%	n	%	n	%	n	%	n
2013	1	33.3	0	0.0	0	0.0	2	66.7	3
2014	0	0.0	1	100.0	0	0.0	0	0.0	1
2015	6	26.1	11	47.8	6	26.1	0	0.0	23
2016	53	18.3	13	4.5	223	76.9	1	0.3	290
2017	50	16.5	15	5.0	237	78.2	1	0.3	303
2013–2017	110	17.7	40	6.5	466	75.2	4	0.6	620

All percentages are row percentages. [a] One additional case was detected in Austria in January 2018 and is not included in the table.

Figure 1. Geographic distribution of *Candida auris* cases reported in EU/EEA countries, 2013–2017 (n=620)[a] [16]



[a] *The map includes one additional case detected in Austria in January 2018, which is not included in the total for the period 2013–2017. Sporadic cases include one case for Austria, one case for Belgium, two cases for France, seven cases for Germany and one case for Norway.*

Two countries experienced four nosocomial outbreaks of *C. auris* affecting a total of 573 patients. The number of cases per outbreak ranged from 39 to 382 according to national reporting. Inter-facility transmission occurred in the four outbreaks, and one outbreak lasted nearly two years. Three outbreaks were controlled whereas one outbreak was still ongoing as of January 2018 [16].

Laboratory capacity and preparedness

Twenty-one out of the 29 EU/EEA countries responding to the ECDC survey on *C. auris* stated that laboratory capability to detect and identify *C. auris* was available, either by formally designated mycology reference laboratories in 12 countries or by laboratories with a reference function in nine countries [16]. Public health measures for preparedness or response to *C. auris* were taken in 20 countries. The most common measures taken were dissemination of laboratory alerts (18 countries) or clinical alerts (10 countries,) and offers for reference identification and antifungal susceptibility testing to hospital laboratories (13 countries). Preparation of guidance for laboratory testing (7 countries), for clinical management (4 countries) or for infection control (4 countries) was undertaken less frequently, and retrospective or prospective surveillance was in place in only a few countries (8 and 7 countries, respectively) [16].

ECDC threat assessment for the EU

Impact on human health

Healthcare-associated *C. auris* infections

Healthcare-associated *C. auris* bloodstream infections have affected patients with severe underlying diseases or immunosuppression, such as patients with diabetes mellitus, chronic kidney disease, HIV-infection, solid tumours and haematological malignancies [7,18]. Neonates have also been affected [8]. However, patients without any underlying severe disease have also been at risk of invasive disease in ongoing outbreaks depending on the affected unit. Patients who developed a *C. auris* infection had frequently been exposed to medical procedures and devices including central venous and urinary catheters, surgery, treatment with broad-spectrum antibiotics, and admission to intensive care units [7,20]. Treatment with systemic antifungals prior to *C. auris* infection has also been reported for several patients [8].

Limited treatment options

Fluconazole and the echinocandins are the antifungal agents most commonly used for the treatment of *Candida* bloodstream infection (candidemia). Both are better tolerated than amphotericin B, which is less often prescribed due to the risk of toxicity. Fluconazole cannot be used for treatment of *C. auris* infection as nearly all isolates are fluconazole-resistant. Resistance to other antifungals seems to be more variable; however, isolates with resistance to all three major classes of antifungals (azoles, echinocandins, and amphotericin B) have been described [22]. This is of concern as it seriously limits available treatment options for patients with invasive *C. auris* infections.

Mortality

Studies have reported a case-fatality rate of *Candida* bloodstream infection of around 30–40%, even in patients receiving antifungal treatment [1,31]. In an invertebrate systemic infection model, the pathogenicity of the most virulent *C. auris* strains was comparable to that of *C. albicans* [32]. There is currently limited information on the case-fatality rate for *C. auris* bloodstream infections due to the small number of patients included in published case series or outbreak descriptions. A study published in 2013 reported case-fatality rates for *C. auris* bloodstream infections of 33% for all patients and 57% for the subgroup of patients admitted to intensive care units, but these rates might be attributable to the severity of underlying diseases in these patients [7]. In the UK outbreak, no fatality could be directly attributed to *C. auris* infection [15,24]. However, as invasive *Candida* infections often occur in severely ill patients with multiple comorbidities, attributable mortality is difficult to determine [24].

Potential for spread

Outbreaks and spread in healthcare settings

Based on molecular typing, transmission of *C. auris* between separate wards that did not share healthcare personnel was reported from a hospital in India [7]. Inter-facility transmission of *C. auris* was also reported in the same study [7] and has occurred in all four outbreaks in the EU/EEA [16]. The majority of *C. auris* infections reported in the published literature were acquired in healthcare settings. The capacity for intra- and inter-hospital spread combined with multi-drug resistance suggest that *C. auris* has the typical characteristics of a healthcare-associated pathogen and further spread in healthcare settings can be expected.

C. auris outbreaks have been difficult to control, with cases in affected hospitals detected over periods longer than a year [11,15]. Widespread environmental contamination of surfaces and equipment surrounding patients carrying *C. auris* has been demonstrated [15,18]. Carriers also represent an important reservoir, and continuous carriage for up to three months after initial isolation of *C. auris* has been documented [18]. Decolonisation was attempted in one outbreak, but colonisation persisted despite daily body washes and oral hygiene with chlorhexidine [15]. There is currently insufficient evidence regarding decolonisation regimens and their effectiveness to eradicate *C. auris* carriage.

Clinicians, infection control staff and microbiologists, even with experience in the control of multidrug-resistant bacteria, may not expect outbreaks of *Candida* species, including *C. auris*. Combined with the additional difficulties with laboratory identification, this lack of awareness might result in outbreaks of *C. auris* remaining unnoticed or only being detected after spread and severe infections have already occurred. It is therefore important to raise awareness and inform clinical and laboratory staff about this emerging threat. As of January 2018, several health authorities in EU/EEA countries had not yet issued such clinical or laboratory alerts [16].

Cross-border transmission

Due to the difficulties with laboratory identification, little is known about the prevalence of *C. auris* in different regions of the world. Nevertheless, C*. auris* isolates, cases and outbreaks have now been reported from five continents: Europe, Asia, North America, South America, and Africa. A recent study showed that isolates of *C. auris* present in the UK have several diverse geographic origins, suggesting multiple introductions into the country [33]. Likewise, whole genome sequencing (WGS) analysis of all clinical *C. auris* isolates reported to the US Centers for Disease Control and Prevention (CDC) from across US hospitals revealed clonal dissemination within several States, of closely related isolates that grouped either with the South Asian clade (New York and New Jersey) or with the South American clade (Illinois) [29]. The increasing number of sporadic cases reported in EU/EEA countries in 2018 [16], compared with 2016 [34] confirms that *C. auris* is repeatedly being introduced into hospitals in Europe, each time with the potential risk for further transmission and healthcare-associated outbreaks among vulnerable patient populations in high-dependency care settings.

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