

Candida auris – focus sur la France

Olivier Lortholary

Centre d'Infectiologie Necker-Pasteur

Université de Paris, Hôpital Necker Enfants malades,
IHU Imagine &

Centre National de Référence Mycoses Invasives &
Antifongiques, Unité de Mycologie Moléculaire,

CNRS UMR 2000, Institut Pasteur, Paris, France.

JNI; 6 Juin 2019



Conflits d'intérêt

Orateur pour Astellas, MSD, Pfizer, Gilead Sciences

Consultant pour Neteos, F2G, Gilead Sciences



Que du
champignon !

Candida auris – information- désinformation!!!

Candida auris sp. nov., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital

Kazuo Satoh^{1,2}, Koichi Makimura^{1,3}, Yayoi Hasumi¹, Yayoi Nishiyama¹, Katsuhisa Uchida¹ and Hideyo Yamaguchi¹

A Candida auris Outbreak and Its Control in an Intensive Care Setting

Eyre et al., New Engl J Med 2019

Invasive Infections with Multidrug-Resistant Yeast Candida auris, Colombia

Morales-Lopez et al., Emerg Inf Dis 2017

The New York Times

A Mysterious Infection, Spanning the Globe in a Climate of Secrecy

The rise of Candida auris embodies a serious and growing public health threat: drug-resistant germs.

First Three Reported Cases of Nosocomial Fungemia Caused by Candida auris

Wee Gyo Lee,¹ Jong Hee Shin,^{2*} Young Uh,³ Min Gu Kang,¹ Soo Hyun Kim,² Kyung Hwa Park,⁴ and Hee-Chang Jang²

Emergence of Candida auris: An International Call to Arms

Clancy and Nguyen, Clin Infect Dis 2017

Desoubeaux et al., J Mycologie Médicale 2018

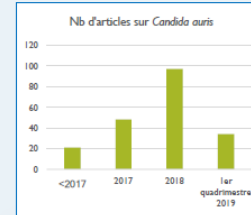
Candida auris in contemporary mycology labs: A few practical tricks to identify it reliably according to one recent French experience

Candida auris : un champignon résistant menace la santé mondiale

Franceinfo

Candida auris : doit-on craindre la propagation en France de ce "champignon tueur" ?

LCI



DAILY STAR

Home | Life & Style | Real Life | Thought yeast infections were harmless? 60% of people die from this vaginal disease

HOME NEWS SPORT SHOWBIZ & TV TRAVEL LIFE & STYLE TECH PICS VIDS

REAL LIFE LOVE & SEX DIET & FITNESS FASHION & BEAUTY HOROSCOPES JUST JANE CARS COMPETITIONS

Thought yeast infections were harmless? 60% of people die from this vaginal disease

A SCARY new strain of yeast infection can be deadly, experts warn.

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10

By Sarah Buchanan / Published 5th July 2016



REAL LIFE



You won't believe what was found growing inside this woman's vagina

YOU won't believe some of these mind-boggling medical marvels and what's been secretly living inside their bodies.



There's something very strange about this bikini body -

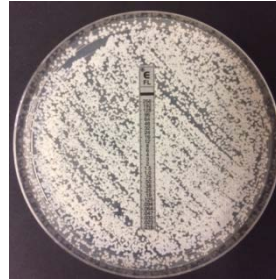
Married woman makes £3k a DAY blackmailing and

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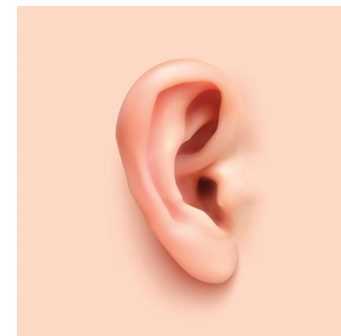
Internet | Protected Mode

Eléments d'inquiétude liés à *Candida auris*



1. Difficult to identify
2. Usually fluconazole resistant, some multi-drug resistant strains
3. High crude mortality reported from some outbreaks
4. Propensity for nosocomial spread patient to patient in high risk settings
5. Persists in the hospital environment
6. Often fails to respond to normal infection control procedures
7. Global spread with simultaneous emergence on at least three continents
8. Now documented from five continents since recognition in 2009

Candida auris



Microbiol Immunol. 2009 Jan;53(1):41-4. doi: 10.1111/j.1348-0421.2008.00083.x.

Candida auris sp. nov., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital.

Satoh K¹, Makimura K, Hasumi Y, Nishiyama Y, Uchida K, Yamauchi H.

JOURNAL OF CLINICAL MICROBIOLOGY, Sept. 2011, p. 3139–3142
0095-1137/11/\$12.00 doi:10.1128/JCM.00319-11
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Vol. 49, No. 9

First Three Reported Cases of Nosocomial Fungemia Caused by *Candida auris*[▽]

Wee Gyo Lee,¹ Jong Hee Shin,^{2*} Young Uh,³ Min Gu Kang,¹ Soo Hyun Kim,²
Kyung Hwa Park,⁴ and Hee-Chang Jang⁴

Department of Laboratory Medicine, Ajou University School of Medicine, Suwon, South Korea¹; Department of Laboratory Medicine, Chonnam National University Medical School, Gwangju, South Korea²; Department of Laboratory Medicine, Yonsei University Wonju College of Medicine, Wonju, South Korea³; and Department of Internal Medicine, Chonnam National University Medical School, Gwangju, South Korea⁴

Candida auris : émergence globale

Sporadic introductions

Simultaneous emergence on 3 continents

Large outbreaks with imported strains



- 2009 Japanese - ear discharge
- Chronic otitis media S. Korea
- Nosocomial blood stream infection Korea , Japan, Malaysia



- Multiple hard to control outbreaks reported from India and Pakistan
- High mortality rates (60%)



- S. Africa/Kenya ongoing nosocomial spread many hospitals
- Several thousand patients
- 70-80 per month



- Venezuela large multi-centre outbreaks
- 38% mortality, neonatal unit 28%
- Columbia 35% mortality



Israel



Norway



Spain



Kuwait



Belgium



UK



Oman



Austria



USA



Germany



China



France



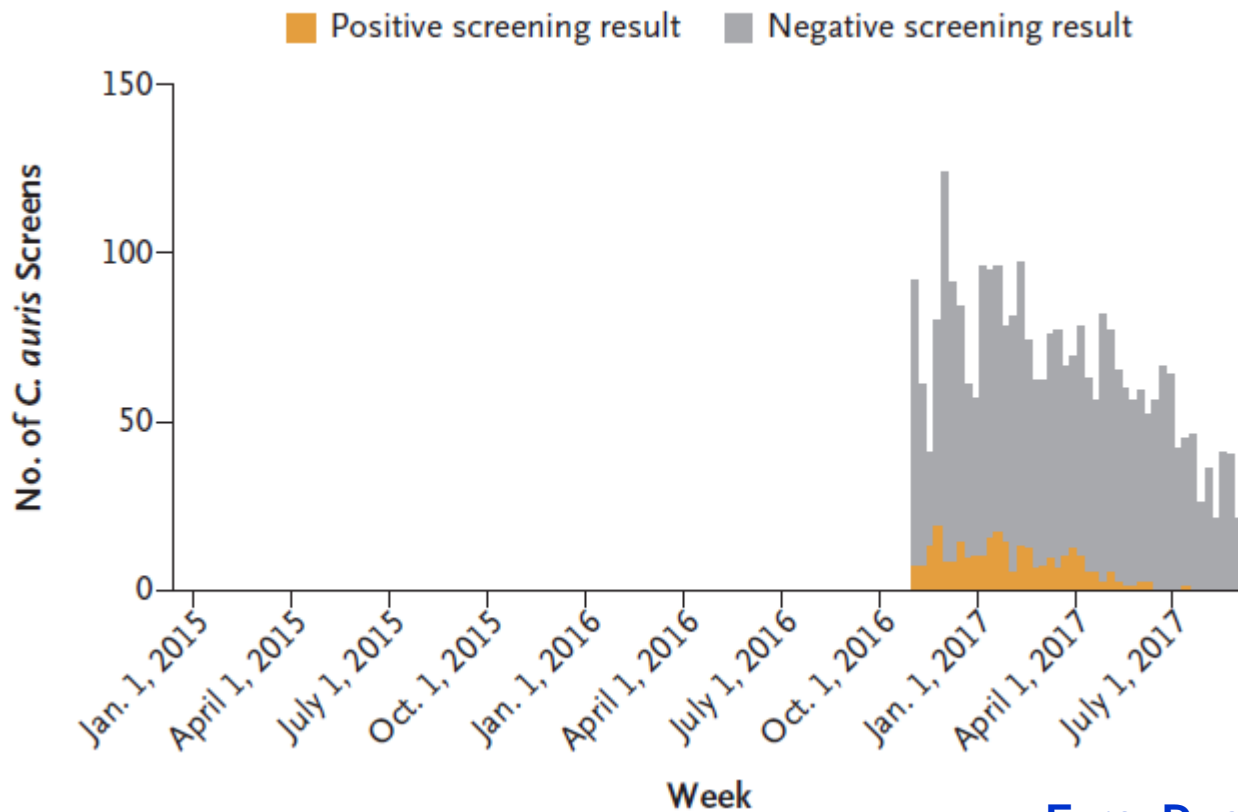
Russia

ORIGINAL ARTICLE

David W. Eyre, D.Phil., Anna E. Sheppard, Ph.D., Hilary Madder, F.A.N.Z.C.A., Ian Moir, Ruth Moroney, M.Sc., T. Phuong Quan, M.Sc., David Griffiths, B.Sc., Sophie George, M.Sc., Lisa Butcher, M.Sc., Marcus Morgan, M.Sc., Robert Newnham, Mary Sunderland, B.Sc., Tiphonie Clarke, B.A., Dona Foster, Ph.D., Peter Hoffman, B.Sc., Andrew M. Borman, Ph.D., Elizabeth M. Johnson, Ph.D., Ginny Moore, Ph.D., Colin S. Brown, F.R.C.Path., A. Sarah Walker, Ph.D., Tim E.A. Peto, F.R.C.P., Derrick W. Crook, F.R.C.Path., and Katie J.M. Jeffery, Ph.D.

A *Candida auris* Outbreak and Its Control in an Intensive Care Setting

B Weekly Rates of Screening for *C. auris*



Estimated cost of screening > \$0.5 million in one London hospital

Candida auris in South Africa, 2012–2016

Nelesh P. Govender, Rindidzani E. Magobo, Ruth Mpenbe, Mabatho Mhlanga, Phelly Matlapeng, Craig Corcoran, Chetna Govind, Warren Lowman, Marthinus Senekal, Juno Thomas

National Institute for Communicable Diseases NICD South Africa

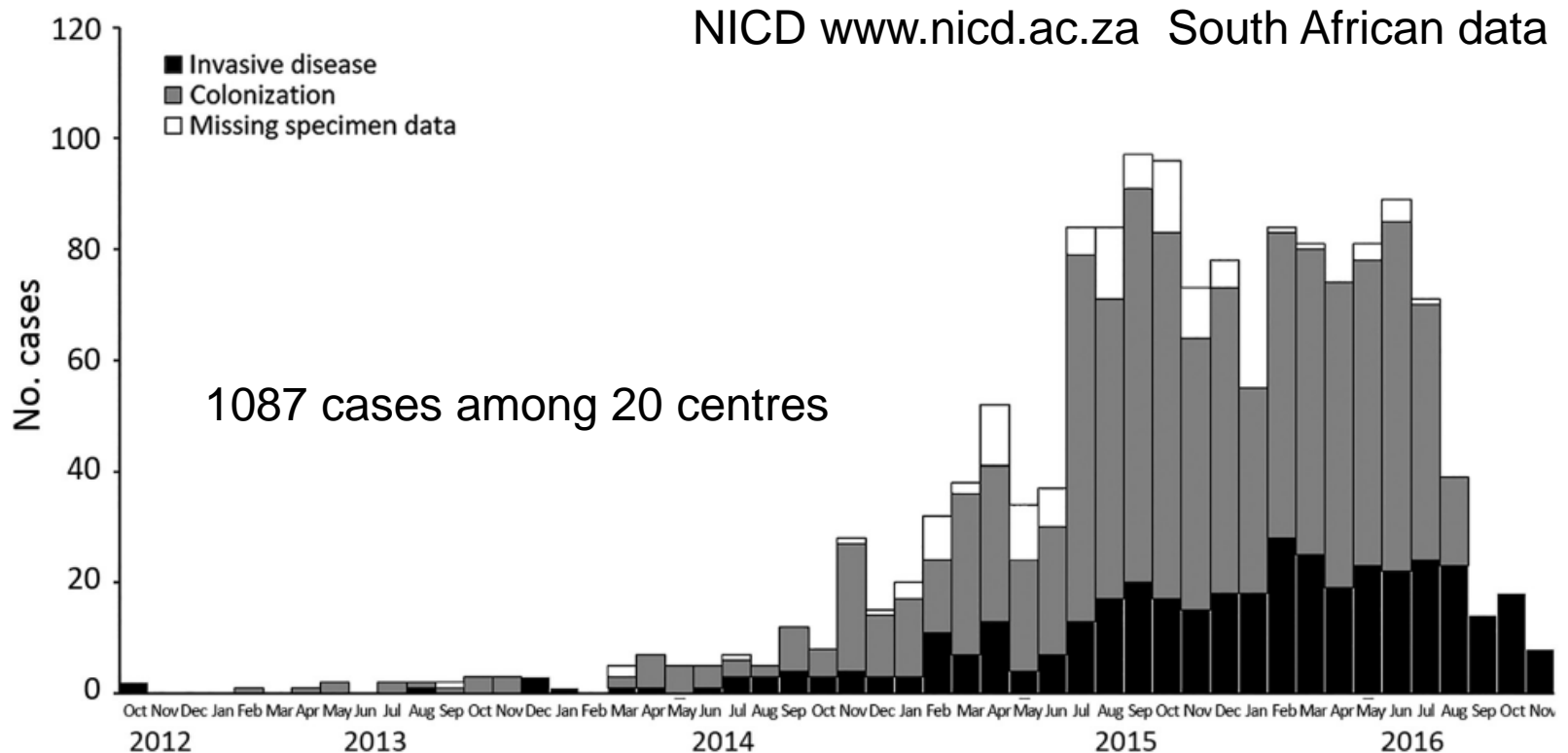
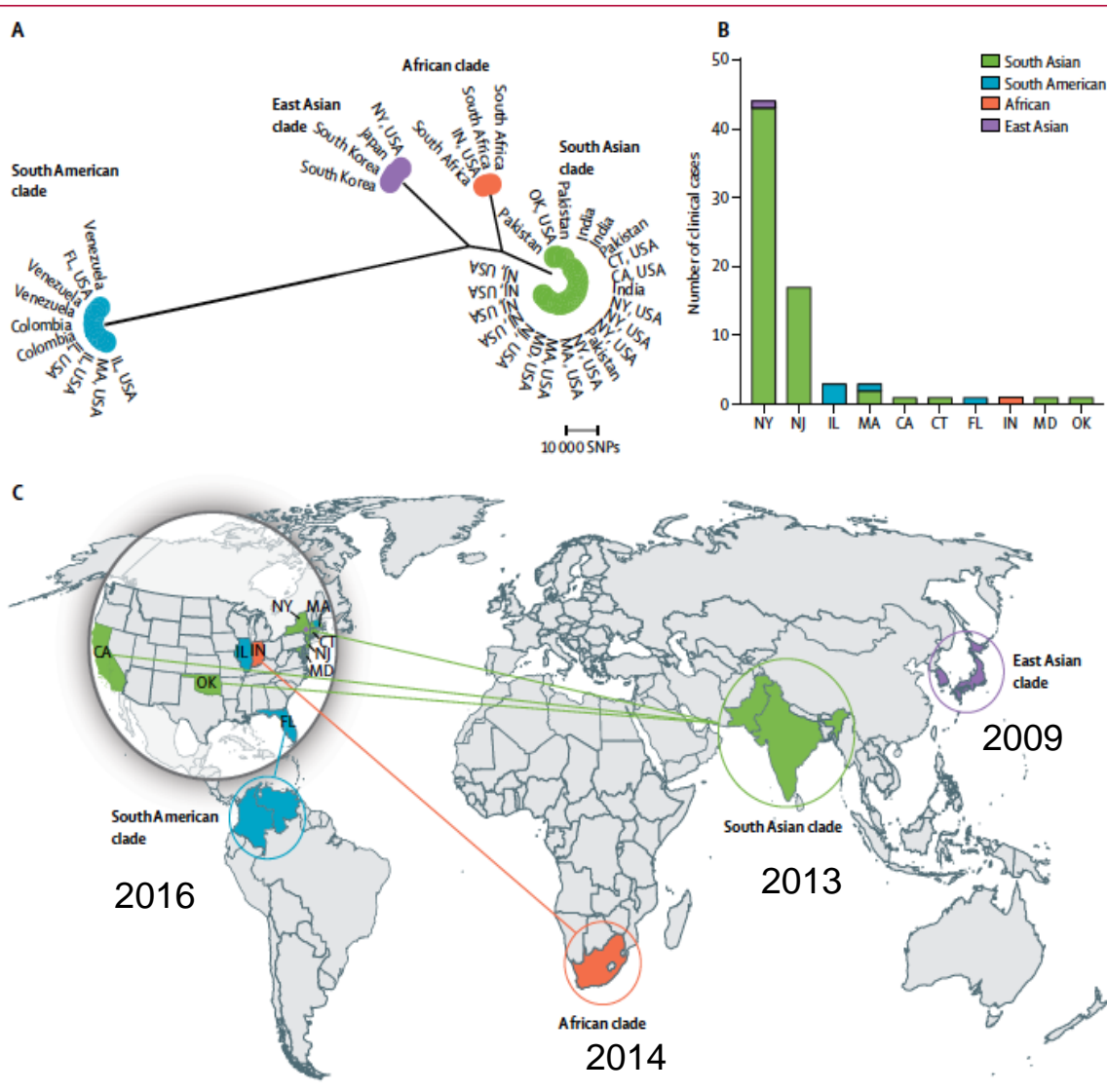


Figure 2. Distribution of cases of *Candida auris* by type of infection and date of specimen collection, South Africa, 2012–2016. n = 1,306.

Epidémies à *C. auris*

Country	Nb outbreaks	WGS
India	3	
Pakistan	1	+
Kuwait	1	
Oman	1	
Saudi Arabia	1	
Israel	1	
South Africa	1	
Colombia	1	
Venezuela	1	
Spain	1	
UK London/Oxford	3	+
USA	2	+

Candida auris: Internationally



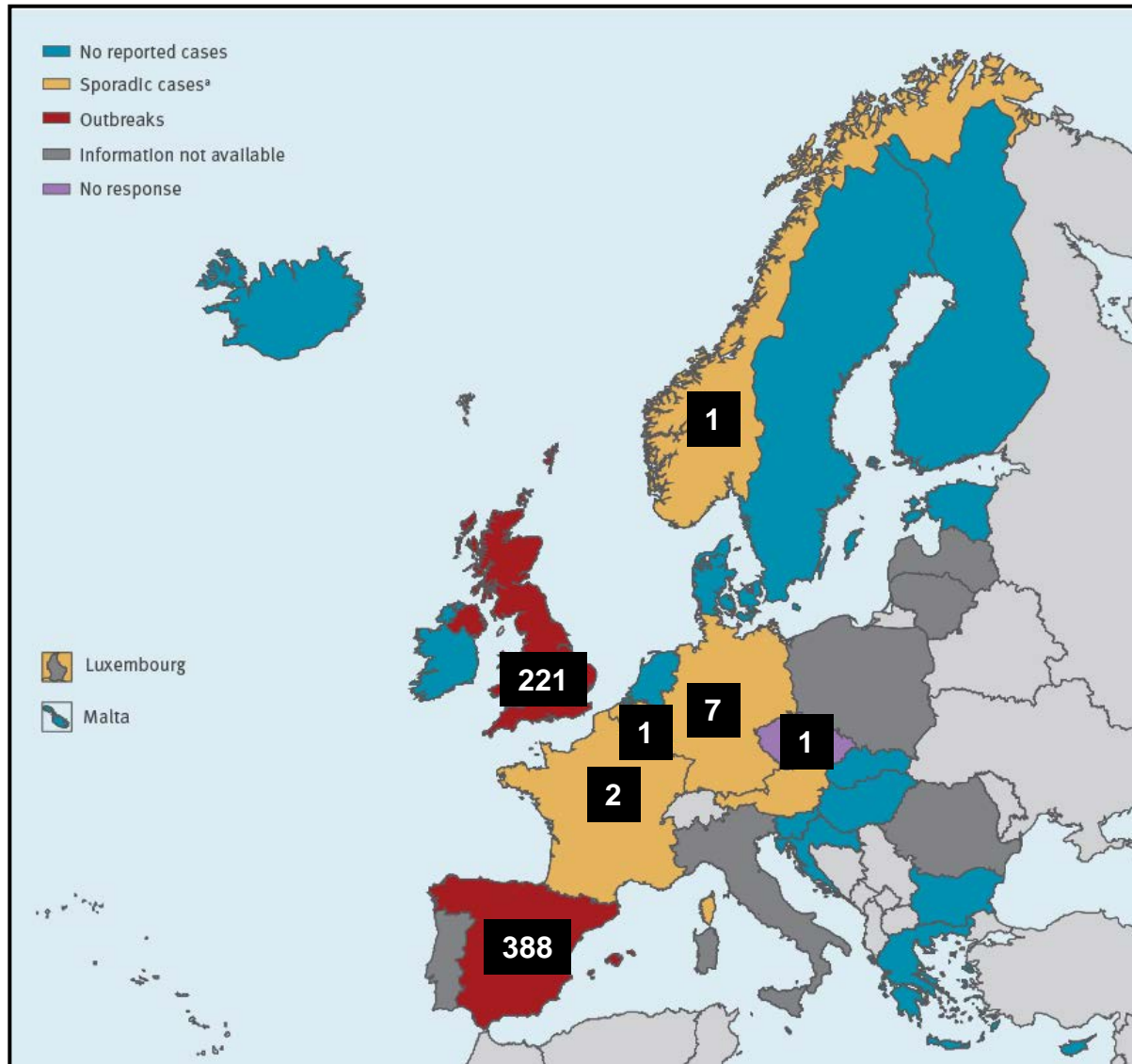
Multiple introductions and subsequent transmission of multidrug-resistant *Candida auris* in the USA: a molecular epidemiological survey.

Chow N.A. *et al.* Lancet Infect Dis 2018

Figure 1: Distribution of *Candida auris* clades within the USA

(A) Maximum parsimony phylogenetic tree of isolates from Colombia, India, Japan, Pakistan, South Korea, South Africa, Venezuela, and clinical cases in the USA (up to the first five clinical cases from each US state). (B) The frequency of clinical cases in the USA by clade. (C) The geographical distribution of clades; solid lines indicate introductions that are associated with patients known to have received health care abroad. CA=California. CT=Connecticut. FL=Florida. IL=Illinois. IN=Indiana. MA=Massachusetts. MD=Maryland. NY=New York. NJ=New Jersey. OK=Oklahoma. SNPs=single-nucleotide polymorphisms.

620 cases of *C. auris* isolation from EU/EEA countries 2013 - 2017



Colonisation
466 (75.2%)

Infection
150 (24.2%)

UK experience:

Multiple independent
introductions
25 UK centres
73 infections
41/73 candidaemia

3 outbreaks – one
ongoing

***Candida auris* infection and colonisation**

Types of infection encountered

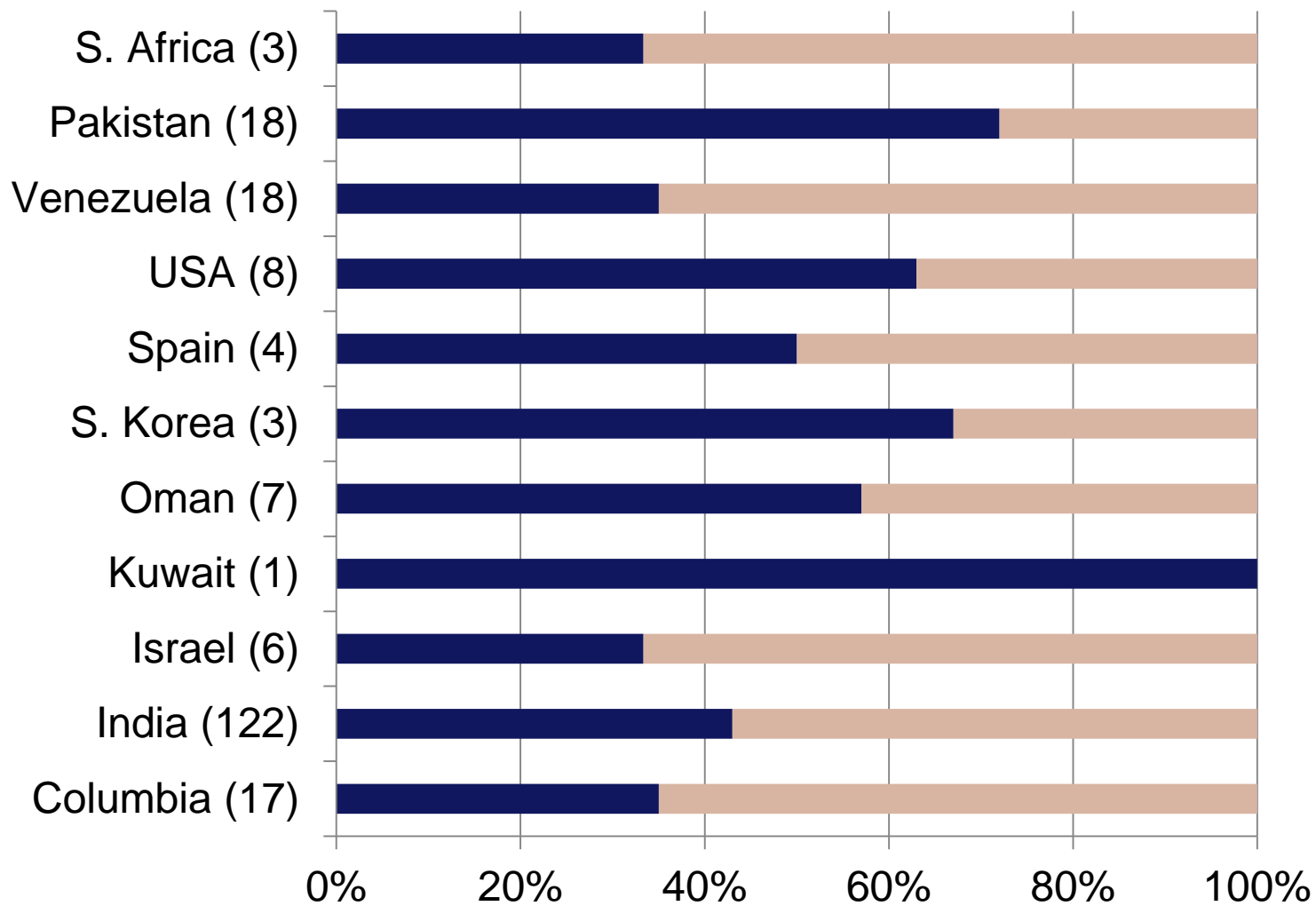
- Candidaemia
- Urinary tract / kidney infection
- Bile infection
- CSF infection
- Wound infection
- Respiratory
- Bone infection
- Ear infection
- Vaginal infection

Colonisation

- Axilla
- Groin
- Nose
- Throat
- Perineum and rectum
- Urine (stool rare)

Crude *Candida auris* mortality rate (%)

Sekyere 2018 Systematic Review e578 1-29



UK isolates to date 73 deep infections; 41 of which BSI no attributable mortality

Most common predisposing factors and conditions for *Candida auris* infection

- Diabetes mellitus (diabetic foot ulcers)
- Chronic kidney disease
- Peripheral vascular disease
- Surgery esp. abdominal, vascular
- Previous healthcare exposure
- Previous broad spectrum antibiotic / antifungal exposure
- Central venous catheter in situ (CVC)
- Total parenteral nutrition (TPN)
- ICU care
- Urinary catheterisation
- Mechanical ventilation / underlying respiratory illness
- Low APACHE II score

Kim *et al.* 2009 CID; Chowdhary *et al.* 2013 EID & EJCMID; Vallabhaneni *et al.* 2016 MMWR; Morales-Lopez *et al.* 2017 EID; Ben-Ami *et al.* 2017 EID; Schwartz *et al.* CDR 2017; Tsay *et al.* 2017 MMWR; Lockhart *et al.* 2017 Arauz *et al.* 2017 Mycoses; Rudramurthy *et al.* 2017 JAC



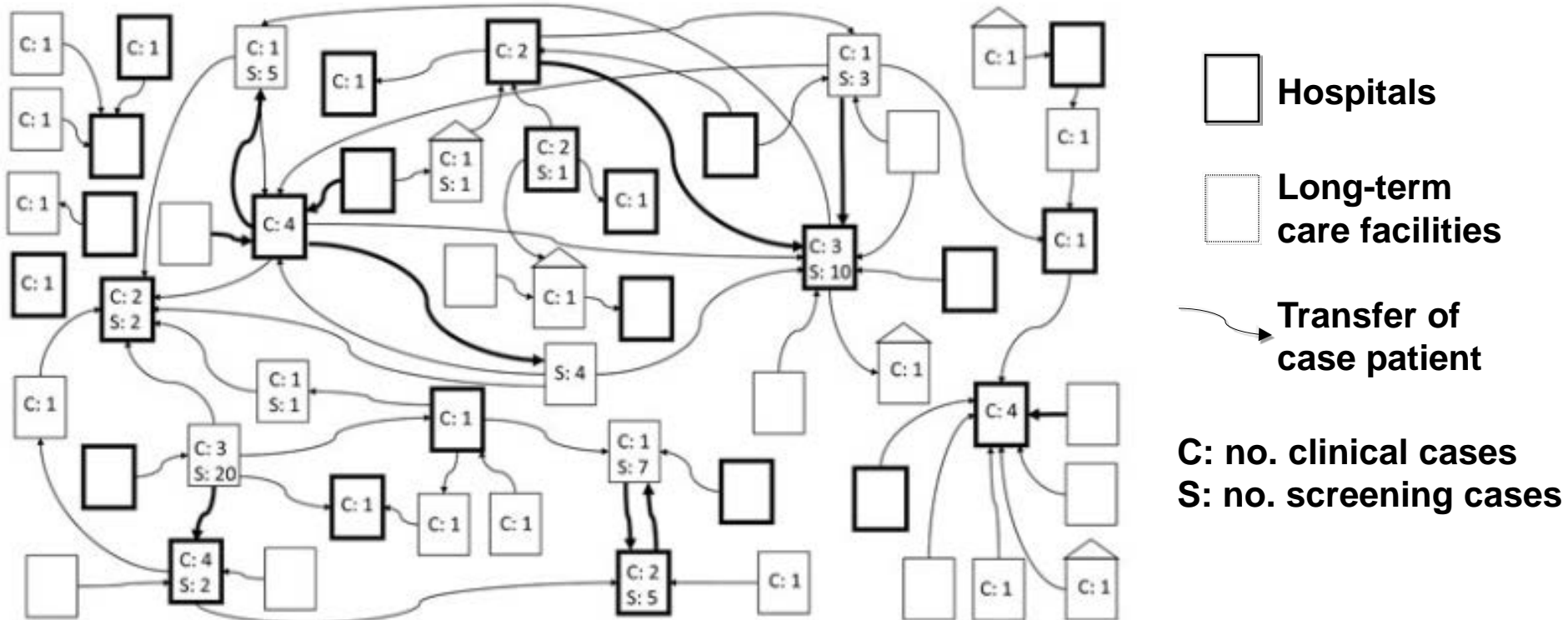
Volume 24, Number 10—October 2018

Research

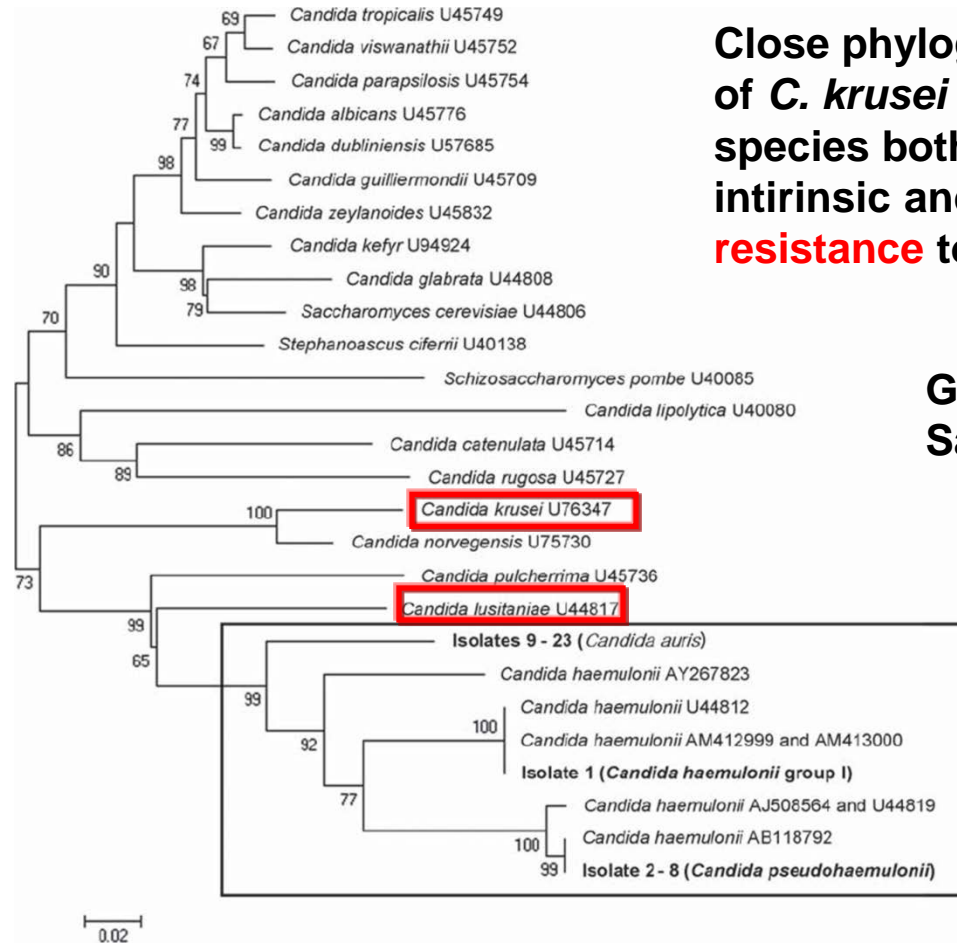
Candida auris in Healthcare Facilities, New York, USA, 2013–2017

Eleanor Adams, Monica Quinn, Sharon Tsay, Eugenie Poirot, Sudha Chaturvedi, Karen Southwick, Jane Greenko, Rafael Fernandez, Alex Kallen, Snigdha Vallabhaneni, Valerie Haley, Brad Hutton, Debra Blog, Emily Lutterloh, Howard Zucker, and Candida auris Investigation Workgroup¹

Figure 2



Candida auris is an ascomycete yeast from the order *Saccharomycetales*



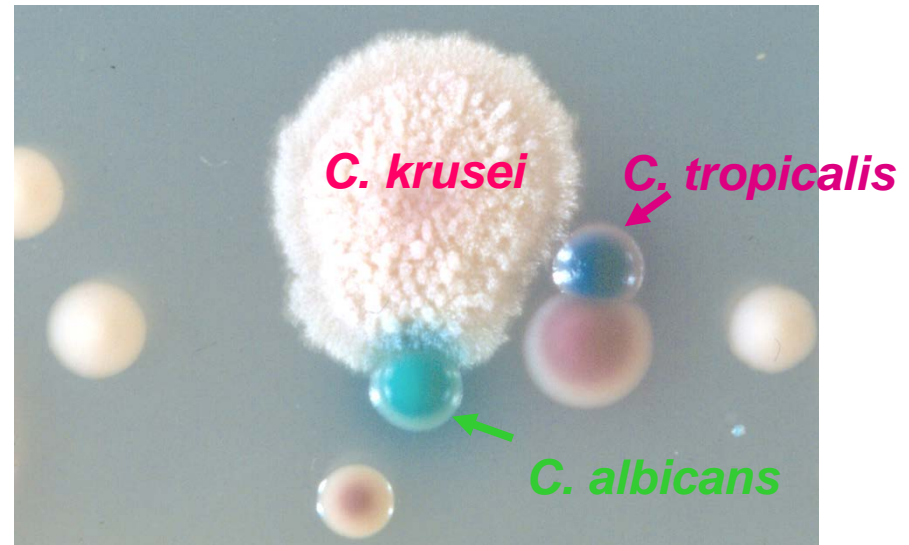
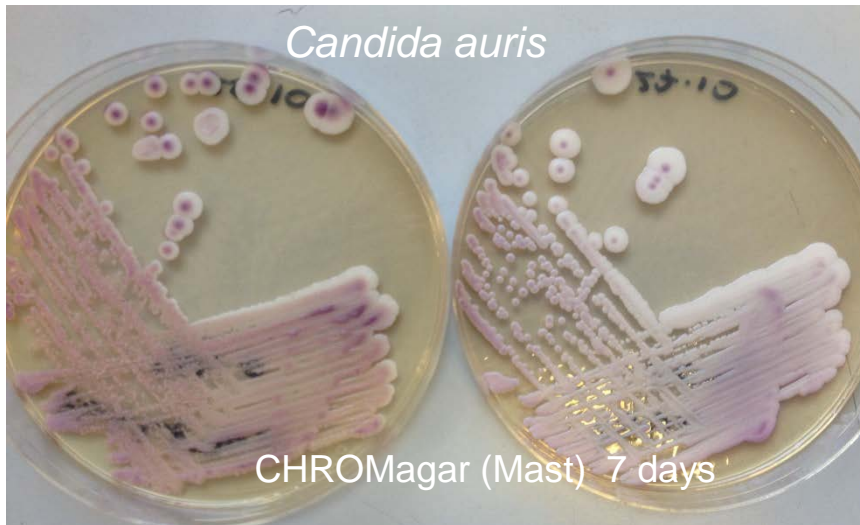
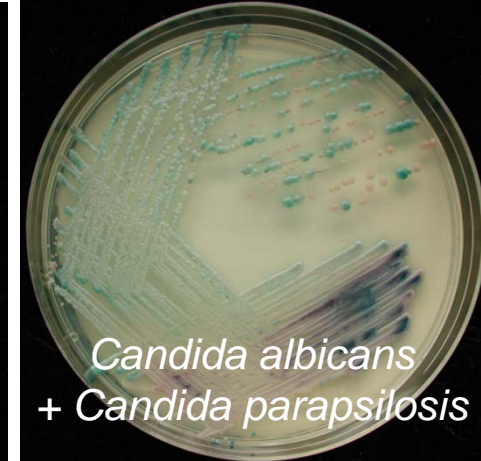
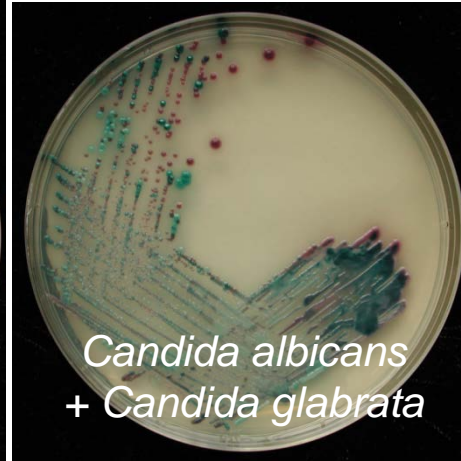
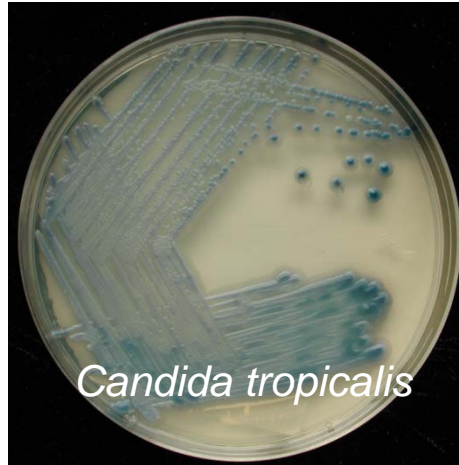
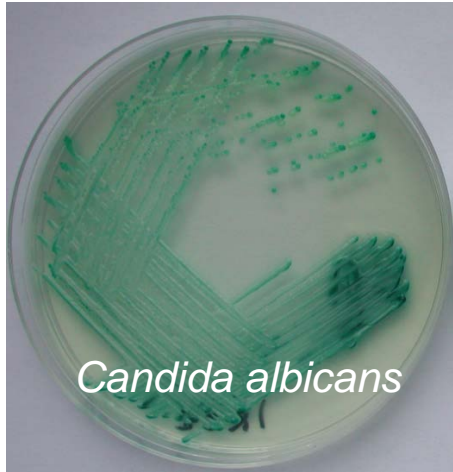
Close phylogenetic relative of *C. krusei* and *C. lusitaniae* species both notable for their intrinsic and inducible **resistance** to antifungal agents

Grows well at 42°C
Salt tolerant

Candida haemulonii complex
(*Metchnikowiaceae*)
Often resistant to amphotericin B

From: Biofilm formation and genotyping of *Candida haemulonii*, *Candida pseudo-haemulonii*, and a proposed new species (*Candida auris*) isolates from Korea. Oh et al. 2011 Med Mycol. 2011;49(1):98-102. doi:10.3109/13693786.2010.493563
Med Mycol | © 2011 ISHAM

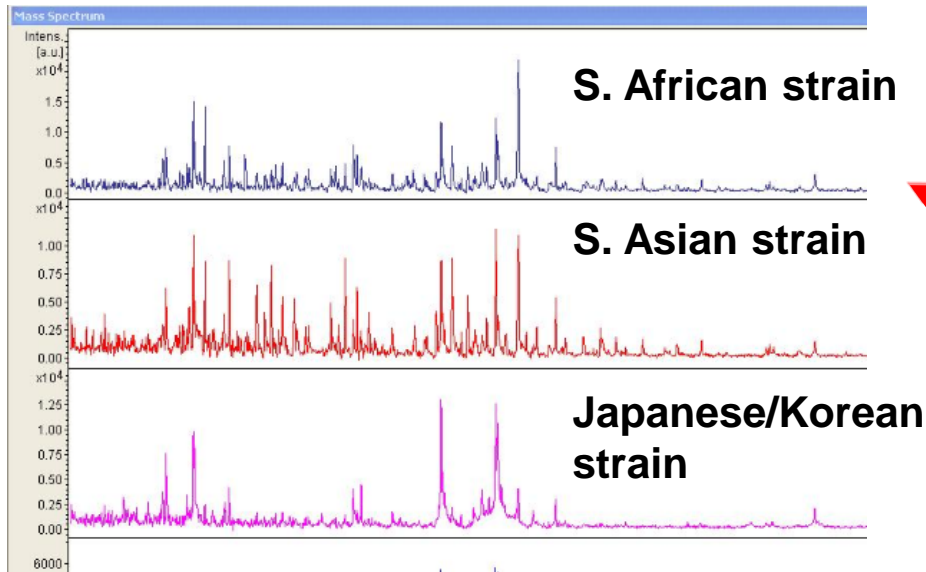
Candida colonies on CHROMagar Candida®



MALDI-TOF

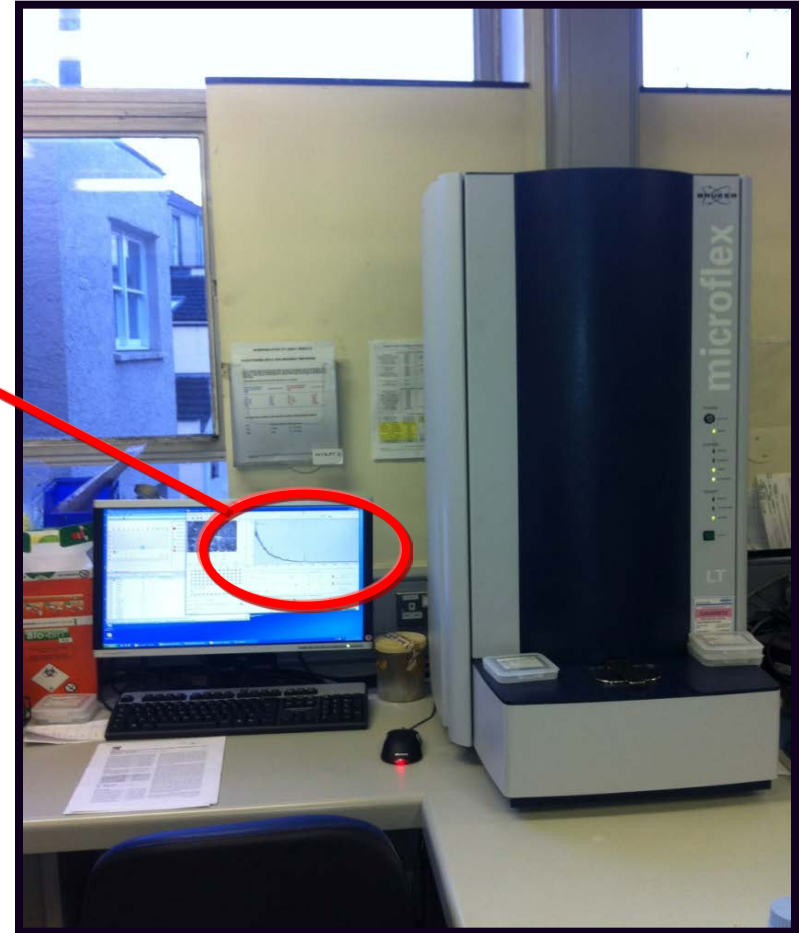
Matrix Assisted Laser Desorption/Ionisation – Time of Flight

Candida auris proteomic profiles



Mis-identifications with most commercial Identification systems:

AUXACOLOR
API20C-AUX
VITEK
BD PHOENIX
MICROSCAN

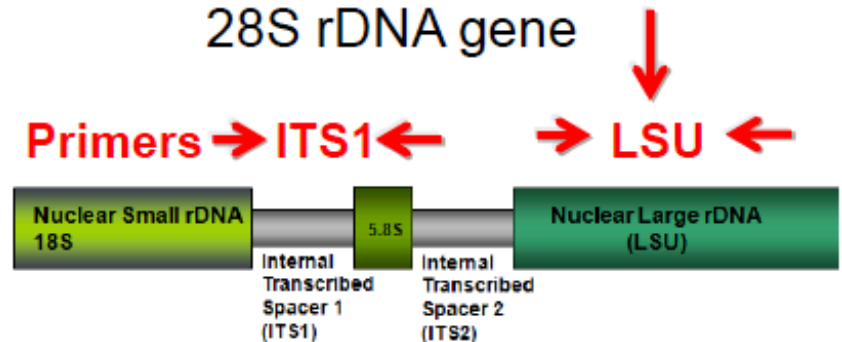


Bruker Microflex MALDI-TOF and Biotyper software BDAL database

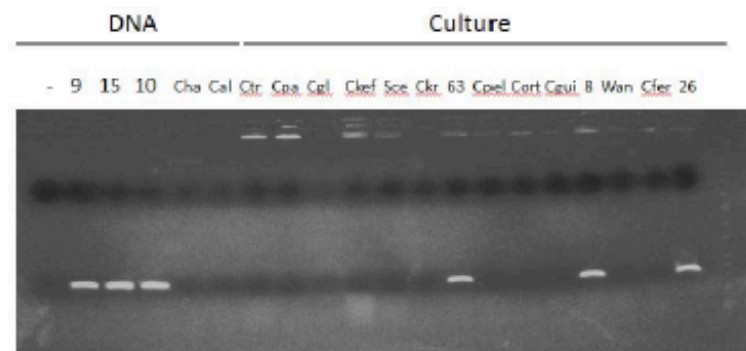
C. auris: rDNA sequencing

ORGANISM	% Identity
<i>Candida auris</i> (Indian clade)	100
<i>Candida auris</i> (African Clade)	99
<i>Candida auris</i> (Japanese/Korean Clade)	99
<i>Candida lusitanae</i>	82
<i>Candida haemulonii</i>	82
<i>Candida guilliermondii</i>	80
<i>Candida ciferii</i>	80
<i>Candida pseudohaemulonii</i>	79
<i>Candida duobushaemulonii</i>	79
<i>Candida tropicalis</i>	79
<i>Candida kefyr</i>	79
<i>Candida pelliculosa</i>	78
<i>Saccharomyces cerevisiae</i>	77
<i>Candida utilis</i>	76
<i>Candida famata</i>	75
<i>Candida parapsilosis</i>	70
<i>Candida magnoliae</i>	46
<i>Candida albicans</i>	43
<i>Candida krusei</i>	43
<i>Candida glabrata</i>	42
<i>Candida inconspicua</i>	42
<i>Candida norvegensis</i>	42
<i>Candida rugosa</i>	39

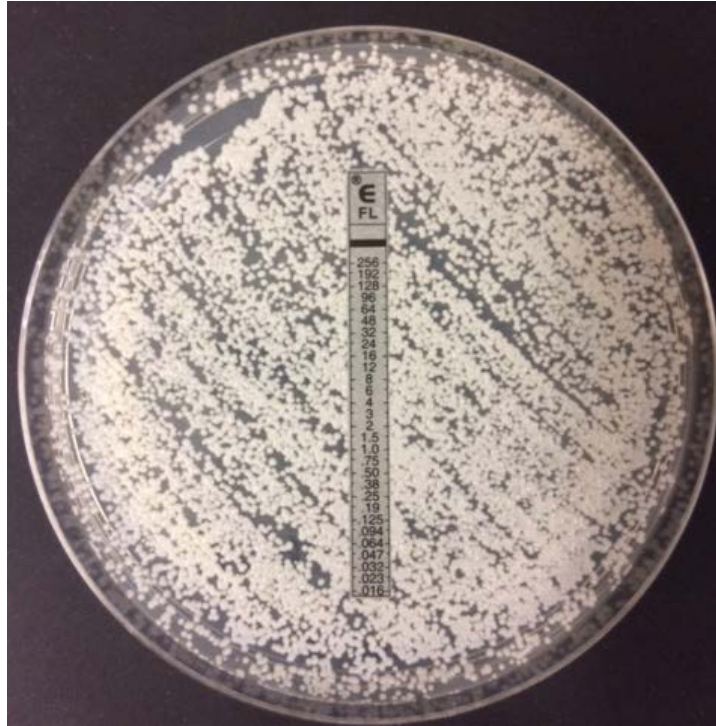
Nucleotide identity over 285 bp D1-D2 portion of 28S rDNA gene



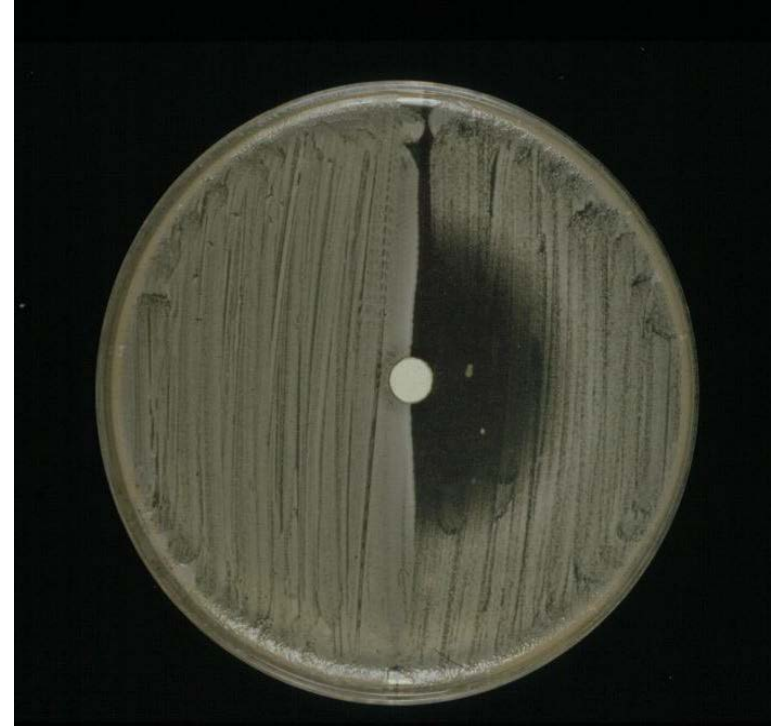
Diagnostic PCR based on ITS region



Isolates of *Candida auris* are almost invariable fluconazole resistant so quick tests can be used to identify resistant yeast isolates



Etest



Disc test
CLSI M44-A

C. auris: antifungal resistance

MIC distributions of *C. auris* isolates, no. of isolates at each MIC

based on *C. albicans* CLSI breakpoints: **Susceptible** **Intermediate** **Resistant** (latest data)

		MIC (mg/L)														(latest data)
		0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	>64	
Amphotericin B (100)	(single)	-	-	-	-	1	2	41	13	-	-	-	-	-	-	17%
	(aggr.)	-	-	-	-	1	16	22	3	1	-	-	-	-	-	
Fluconazole (101)	(single)	-	-	-	-	-	-	-	-	-	5	25	10	6	13	100%
	(aggr.)	-	-	-	-	-	-	-	-	-	-	-	-	-	42	
Itraconazole (43)	(single)	-	20	5	1	2	2	-	-	-	-	1	-	-	-	5%
	(aggr.)	-	-	-	-	7	4	1	-	-	-	-	-	-	-	
Voriconazole (98)	(single)	-	-	10	17	13	9	3	1	1	-	2	-	-	-	43%
	(aggr.)	-	-	-	-	1	3	13	13	10	1	1	-	-	-	
Posaconazole (44)	(single)	-	21	7	1	1	-	-	1	-	-	1	-	-	-	10%
	(aggr.)	-	-	9	2	1	-	-	-	-	-	-	-	-	-	
Caspofungin (13)	(all)	-	-	1	6	3	1	-	1	-	-	-	1	-	-	20%
Anidulafungin (89)	(single)	4	3	14	13	9	-	2	2	2	-	-	-	-	-	8%
	(aggr.)	-	-	13	17	6	2	1	1	-	-	-	-	-	-	
Flucytosine (58)	(single)	-	-	26	3	3	-	1	-	3	2	2	2	-	5	14%
	(aggr.)	-	-	6	3	-	1	1	-	-	-	-	-	-	-	

C. auris: environmental contamination



Survival of *Candida auris* on surfaces > 14d

Welsh et al. 2017 *J. Clin. Micro* 55:10;2996 – 3005

Hygiène hospitalière



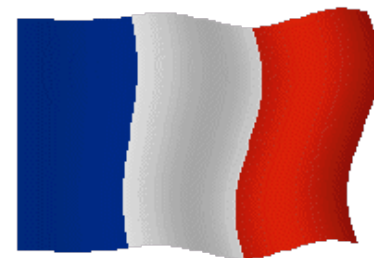
Environment: Chlorine-based disinfectant
Hydrogen peroxide fogging for rooms once empty

- Chlorhexidine as the topical antiseptic - chlorhexidine baths
Chlorhexidine plus isopropyl more effective Iodine based skin disinfectant

Moore et al J. Hosp. Infect 2017

Surveillance de toutes les infections fongiques invasives en France

Envoi de tous les isolats d'espèces non fréquentes pour re-identification au CNR (MALDI-ToF et séquençage)



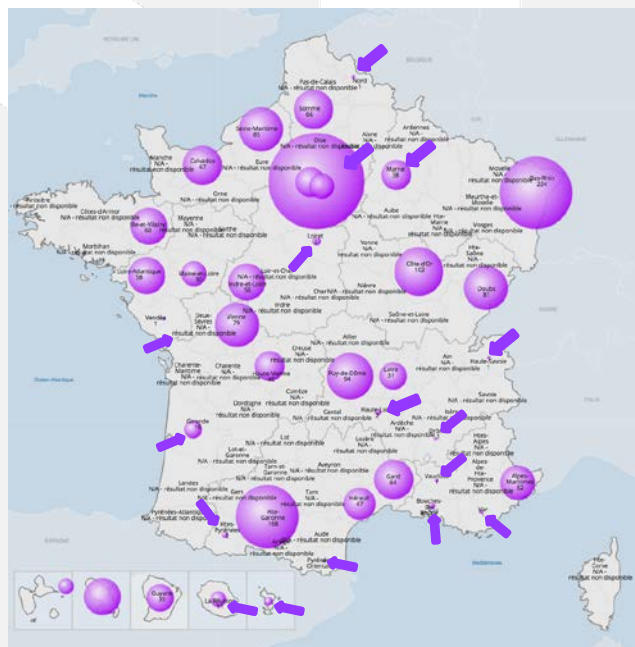
Fongémies

5576 dans l'ODL depuis 2002

5372 dans RESSIF depuis 2012

Isolats de *C. auris* en France (\pm CNRMA)

- 3 cas prouvés (une fongémie chez un patient hospitalisé à La Réunion en 2015, et deux colonisations (en 2017 à Tours*, et un en 2019 à La Réunion).
- 2 cas probables (2 colonisations, en 2015 et en 2016, à La Réunion), transmission nosocomiale entre deux cas de 2015.
- Rétrospectivement 1 abcès du foie en **2007** à Paris



Actions du CNRMA après l'alerte du CDC fin juin 2016

1. Alerte du CNRMA le 9 juillet 2016 à tous les mycologues français

Cher(e)s collègues et ami(e)s

Le CNRMA et la SFMM souhaitent porter à l'attention des mycologues français l'alerte que le CDC américain lance sur les infections à *Candida auris*. Le CNRMA n'a eu connaissance que deux cas d'infections invasives toutes les deux associées à des abcès profonds (l'une en 2007, l'autre en 2015). Les deux souches avaient des CMI très hautes pour le fluconazole mais seulement modérément augmentées pour les autres azotés testés (voriconazole et posaconazole), et pour les échinocandines.

Si d'autres cas d'infections invasives étaient diagnostiqués dans vos centres, il est important que le CNRMA puisse colliger les cas et tester les souches avec la technique EUCAST

2. Nouvelle alerte du CNRMA en novembre 2016 en lien avec SPF

... *Si des cas d'infections invasives étaient diagnostiqués dans vos centres, il est important que le CNRMA puisse colliger les cas et caractériser les souches. A noter que cette espèce est facilement confondue avec Candida haemulonii.*

3. Envoi des profils MALDI-TOF de nos souches à la base inter-CHU (R. Piarroux), et contact avec les fabricants Brücker, BioMérieux et Andromas

Probablement utile à Tours, 31 août 2017...

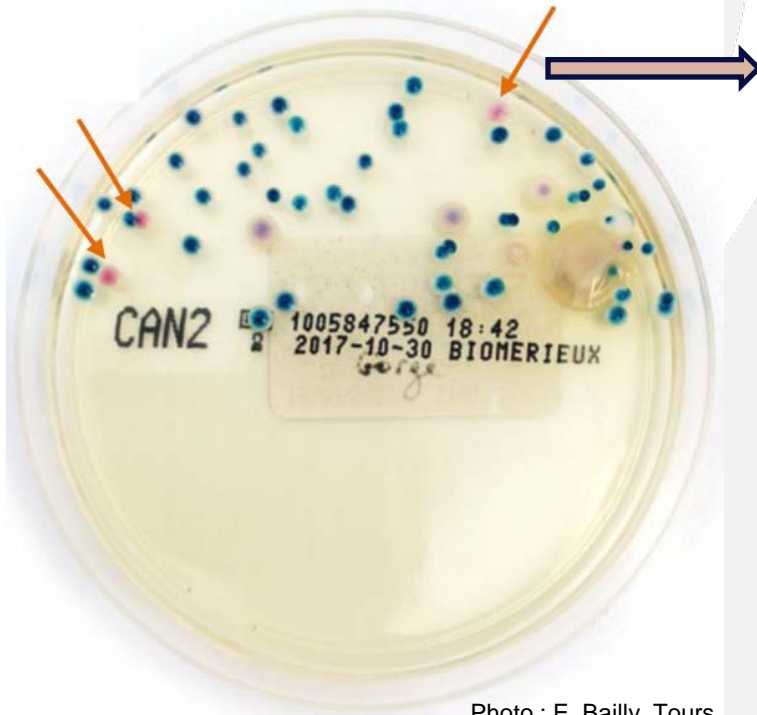


Photo : E. Bailly, Tours

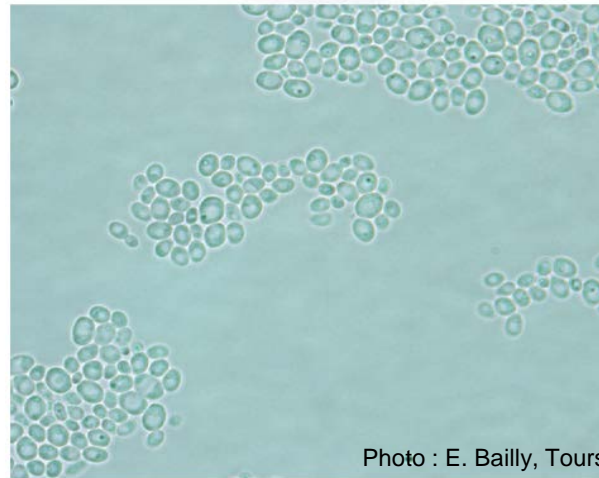


Photo : E. Bailly, Tours

Levure d'aspect banal sur les milieux de culture habituels

Ecouvillon buccal : *C. albicans* + *C. tropicalis* + *C. glabrata*, + quelques colonies de ???

♂ 58 ans

Bilan pré-transplantation en Iran et Inde
Hospitalisé pour transplantation hépatique

Porteur bactéries multi-résistantes*

- + *Escherichia coli* carbapénémase
- + *Enterococcus faecium* vancomycine-R
- + *Escherichia coli* BLSE

Mesures prises à Tours ...

1. Isolement du patient à cause des BMR
2. Envoi de la souche au CNR pour suspicion de *C. auris* en raison des identifications fantaisistes
3. Cartographie positive (gorge, anse intestinale, rectum, urines) mais aucune hémoculture (0/23)
4. Décontamination du laboratoire * :
 - Confinement des cultures (sacs plastiques)
 - Traitement des surfaces et des sols (javel 2,6%)
 - Décontamination des PSM (UV, nettoyage)

*Welsh et al. J. Clin. Microbiol 2017

Quel est le risque de méconnaître un cas ?

1. Risque lié aux techniques et aux bases de données *

- Auxanogramme API20C® (BioMérieux) : *Rhodotorula glutinis* (id.= 98,3%)
- Auxanogramme ID32C® (BioMérieux) : *Candida sake* (id. = 98,1%)
- Système Vitek 2® compact (BioMérieux) : *Candida famata*
 - **Maldi-TOF (Brucker)**: *Candida auris* mais mauvais score (<2)
 - **Maldi-TOF (VITEK MS)** : *pas d'identification* car espèce absente actuellement (mais sera dans la V3.2 base IVD et est présente la 4.15 de la base recherche RUO)

• 2. Risque lié aux procédures

De nombreux laboratoires n'identifient pas les espèces non *albicans*

* Mizusawa et al. J. Clin. Microbiol. 2017

Sensibilité diminuée aux antifongiques

	CMI (mg/L) déterminées par la méthode EUCAST						
	Fluconazole	Voriconazole	Posaconazole	AmphotericinB	Flucytosine	Caspofungine	Micafungine
<i>C. albicans</i> (n=3007)	0.25/0.5	≤0.01/≤0.01	0.03/0.06	0.06/0.12	≤0.12/0.5	0.03/0.06	0.03/0.03
<i>C. auris</i> (n=54) CLSI technique*	128/256 [4 - 256]	2/8 [0.03 - 16]	0.5-1 [0.06 - 1]	1/2 [0.38 - 4]	0.125/0.5 [0.125 - 128]	0.25/2 [0.03 - 16]	0.25/2 [0.06 - 4]

* Lockhart et al. Clin. Infect. Dis. 2017

Sensibilité diminuée aux antifongiques

	CMI (mg/L) déterminées par la méthode EUCAST						
	Fluconazole	Voriconazole	Posaconazole	AmphotericinB	Flucytosine	Caspofungine	Micafungine
<i>C. albicans</i> (n=3007)	0.25/0.5	≤0.01/≤0.01	0.03/0.06	0.06/0.12	≤0.12/0.5	0.03/0.06	0.03/0.03
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<i>C. auris</i> CNRMA7.797	≥64	0.5	0.125	0.5	0.25	0.06	0.5
<i>C. auris</i> CNRMA15.337	≥64	0.125	≤0.014	0.25	≥64	0.015	0.03
<i>C. auris</i> CNRMA17.624	≥64	0.5	≤0.014	0.5	≥64	0.03	0.06
<i>C. auris</i> CBS10913	2	≤0.014	≤0.014	0.06	≤0.125	0.015	0.015

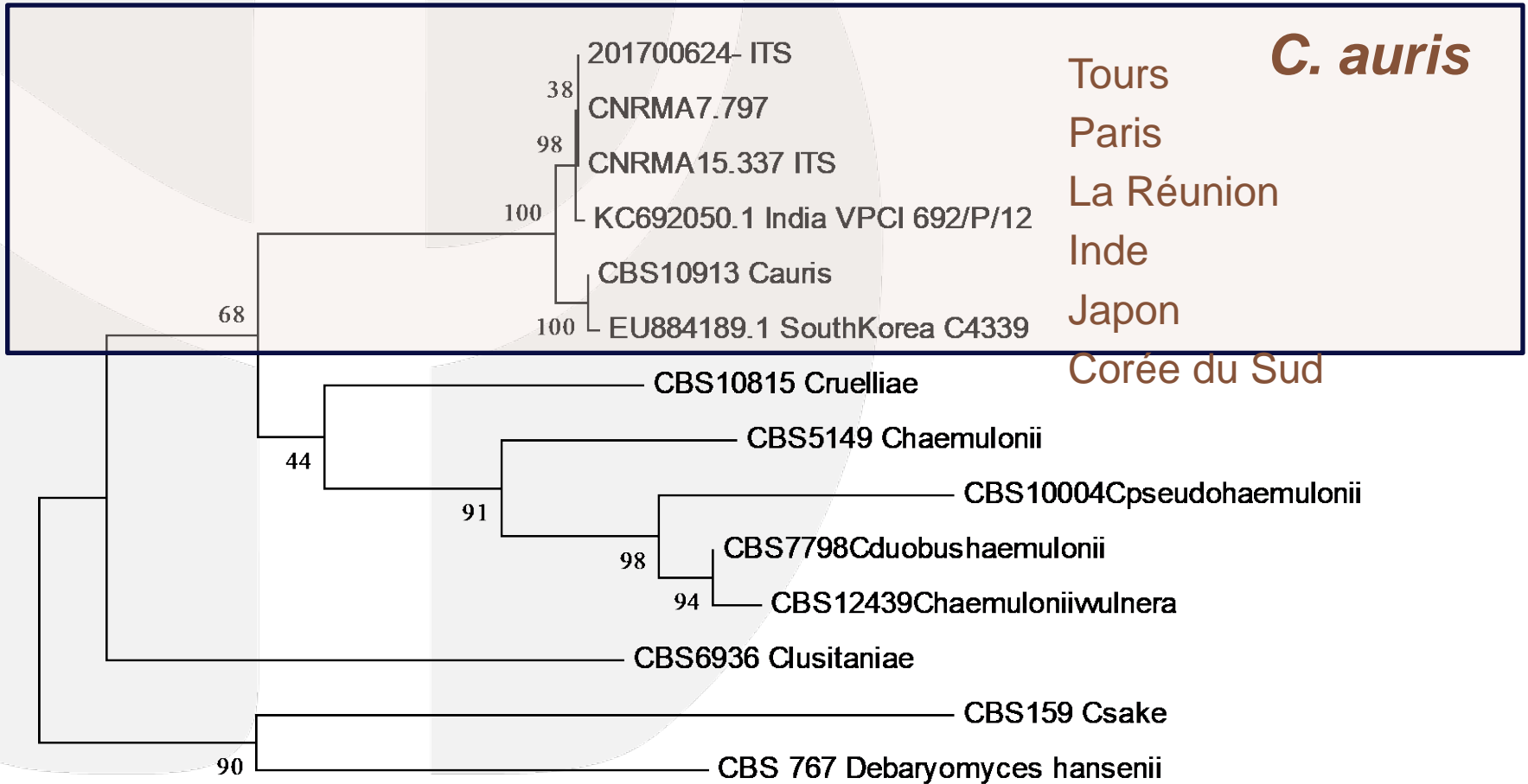
* Lockhart et al. Clin. Infect. Dis. 2017

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<i>C. auris</i> CBS10913	2	≤0.014	≤0.014	0.06	≤0.125	0.015	0.015
<i>C. haemulonii</i> (n=39)	32/≥64	≥8/≥8	2/≥8	0.5/2	≤0.12/0.25	0.03/0.06	0.06/0.12
<i>C. duobushaemulonii</i> (n=38)	32/≥64	≥8/≥8	4/≥8	2/8	≤0.12/≥ 64	0.03/0.03	0.03/0.06
<i>C. palmiroleophila</i> (n=20)	8/32	0.12/0.25	0.12/0.25	0.12/0.5	≤0.12/0.5	0.06/0.25	0.03/0.25
<i>C. krusei</i> (n=312)	32/64	0.25/0.5	0.12/0.25	0.12/0.25	2/4	0.12/0.25	0.06/0.12

* Lockhart et al. Clin. Infect. Dis. 2017

Relation phylogénique



0.05

Envoi au CNRMA en URGENCE pour identification / confirmation si ...

Dans le contexte d'émergence possible de *C. auris*, il est important d'identifier les espèces pour mettre en place les mesures d'isolement adéquates

1. Hospitalisation récente >1 j dans un pays ayant déclaré des épidémies de *C. auris*
A fortiori si colonisation ou infection par une BMR *
2. Si espèce non-*albicans*
 - Identifiée comme *C. haemulonii*, *C. dobuhaemulonii*, *C. sake*, *C. famata* par Vitek2/Auxacolor/Api
 - Ou non identifiée par MALDI-TOF
 - *A fortiori* si sensibilité diminuée au fluconazole
3. Si espèce identifiée *C. auris*

* Eyre et al. N. Engl. J. Med. 2018

Conclusion: *Candida* haut *risque*

Sur le plan international:

1ere évidence d'introduction multiple et indépendante, mondiale, d'une espèce de *Candida*, suivie de transmission nosocomiale

Différentes populations clonales avec virulence/sensibilité in vitro variables ;
acquisition rapide de résistance croisée

Sur le plan national:

Tout cas d'infection ou de colonisation à *Candida auris* doit faire l'objet d'un signalement e-Sin et auprès du CNRMA

CNRMA:

- envoi souches suspectes ou identifiées comme *C. auris* pour confirmation ou identification en urgence (<3h).
- déterminer le profil de sensibilité aux antifongiques (EUCAST).

Enquete sur voyages dans zones à haut risque + isolement/cohorting des pts porteurs avec mesures hygiènes accrues, détection des contacts + désinfection locaux

Echinocandine en 1ere intention si infection invasive