Nursing home associated fungal infection and resistance

National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

Julia (Jianhua) Zhang

Mycology team project leader in RIVM

Nursing home

Vulnerable

- The elderly 80+
- Certain level of sickness- weakened immune system
- Targeted group with the usage of multi-medicine
- The environment is often less controlled than in hospitals.
- Continuously cycling infected patients, or those who carry the germ, into hospitals and back again
- Medical care in nursing homes typically includes a high number of intrusive devices like catheters, cannulas, and feeding tubes. Improper sanitation when inserting these devices increases the risk of contracting fungi.

Fungal infection in Nursing home

- Fungal infections are common in nursing homes - mainly superficial.
- Usually due to *Candida* or dermatophytes.
- *Candida* may affect patients' skin, nails, and mucosa.
- Dermatophytes cause infection of skin, hair and nails.
- Transmission via (in)direct contact or skin flakes; may cause outbreaks
- Antifungal therapy may not be effective due to various reasons:
  - Low compliance
  - Poor drug penetration at the infection site
  - Antifungal resistance

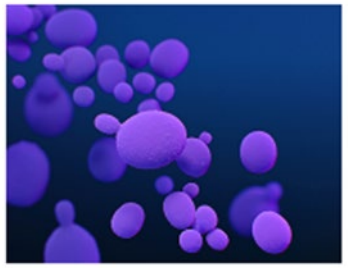
Why fungi develop antifungal resistance

- Improper use of antifungal medicines: When you skip doses, stop treatment too soon or receive a dose that’s too low, a fungus gets better at fighting off the medicine’s effects.
- Antibiotic use: Antibiotics kill harmful bacteria. But they can also kill helpful bacteria in the digestive tract. As a result, Candida, a yeast naturally found inside the digestive tract, can start to grow too fast. A person taking antibiotics may then need antifungals to treat a yeast infection called candidiasis. Frequent treatment raises the risk of drug resistance to both treatments.
- Fungicide use: People who work closely with crops treated by fungicides may be more prone to fungal infections that are antifungal-resistant. In these environments, fungi have increased exposure to fungicides. Fungicides are a type of antifungal that keeps crops from getting moldy.
- Natural resistance: Certain fungi never respond to antifungals. They’re naturally resistant to medicines.
- Spontaneous resistance: A fungus stops responding to a once-effective medicine for no known reason.
- Transmitted resistance: You can spread a contagious drug-resistant fungal infection to someone else. That person now has an infection that won’t respond to an antifungal, even if they’ve never used the medicine.

apple.news

A fatal fungus is spreading among patients in some U.S. nursing homes

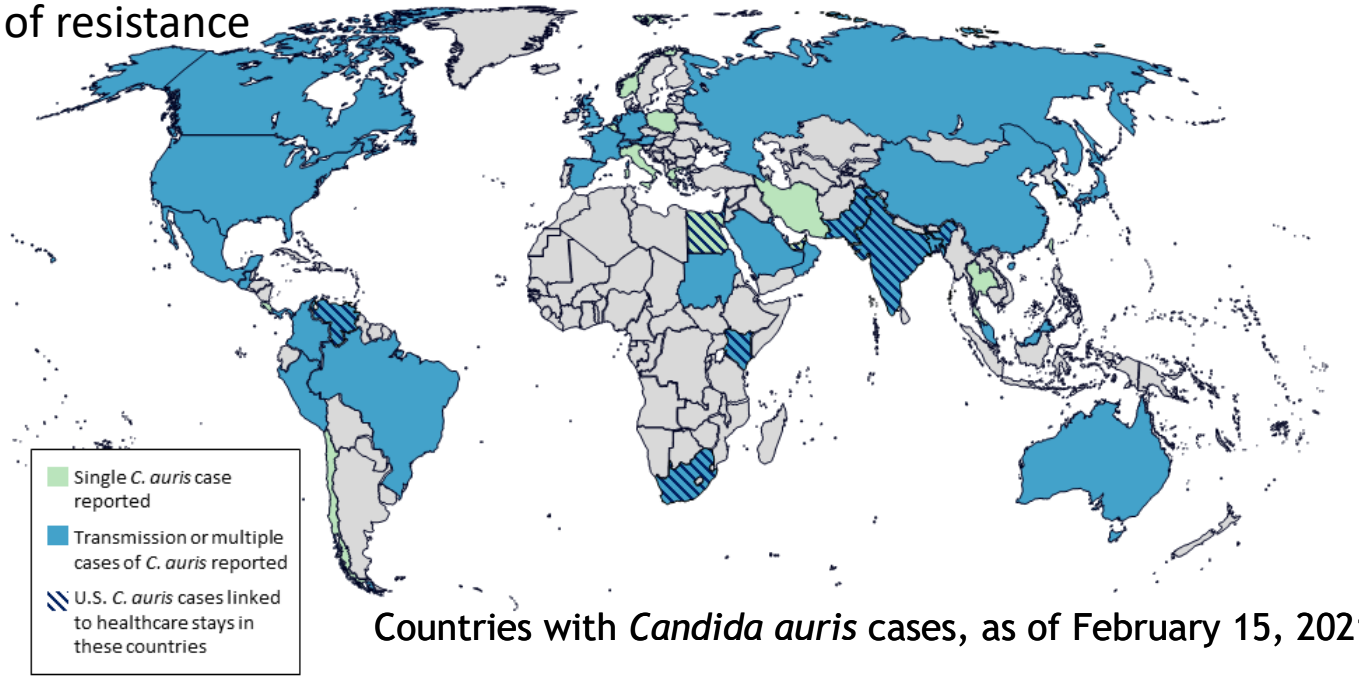
Candida auris



- Infected nearly 800 people since its arrival in the United States four years ago.
- Death rate is 50% within 90 days. 400/800 died
- An additional 1,540 people carry the yeast without showing any symptoms of infection.
- New York, Chicago, and New Jersey nursing homes
- Fever and chills are the first warning signs that an infection is present. If an infection doesn't respond to antibiotics, doctors may suspect the presence of the *C. auris* fungus.

Candida auris

- Emerging pathogen first recognized in 2009
- Difficult identification, misidentification leads to inappropriate treatment – no longer true
- It has caused outbreaks in healthcare settings worldwide
- Infects people who are already sick and hospitalized, with older populations in long-term care facilities at particular risk.
- Multidrug-resistant
- Multiple (unknown) mechanisms of resistance
- Ecological reservoir unknown



Countries with *Candida auris* cases, as of February 15, 2021

From: https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html

Increasing number of cases and outbreaks caused by *Candida auris* in the EU/EEA, 2020 to 2021

Anke Kohlenberg[1] , Dominique L Monnet[1] , Diamantis Plachouras[1] , *Candida auris* survey collaborative group[2]
1. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
2. The members of the *Candida auris* survey collaborative group are listed under Collaborators and at the end of the article

Correspondence: Anke Kohlenberg (anke.kohlenberg@ecdc.europa.eu)

TABLE 1

Reported cases of *Candida auris* infection or carriage, EU/EEA, 2013–2021 (n = 1,812)

Country	2013	2014	2015	2016	2017	2018	2019	2020	2021	2013–2021
Austria	0	0	0	0	0	1	0	2	1	4
Belgium	0	0	0	1	0	0	3	0	1	5
Bulgaria	0	0	0	0	0	0	0	0	0	0
Croatia	0	0	0	0	0	0	0	0	0	0
Cyprus	0	0	0	0	0	0	NA	NA	NA	NA
Czechia	0	0	0	0	0	0	1	0	0	1
Denmark	0	0	0	0	0	0	0	0	2	2
Estonia	0	0	0	0	0	0	0	0	0	0
Finland	0	0	0	0	0	0	0	0	1	1
France[a]	0	0	2	1	1	0	3	4	4	15
Germany	0	0	2	0	5	2	3	5	10	27
Greece	0	0	0	0	0	0	3	13	58	74
Hungary	0	0	0	0	0	0	0	0	0	0
Iceland	0	0	0	0	0	0	0	0	0	0
Ireland	0	0	0	0	0	0	0	0	1	1
Italy	NA	NA	NA	NA	NA	NA	1	49	242	292
Latvia	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Liechtenstein	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lithuania	NA	NA	NA	NA	NA	NA	NA	0	0	0
Luxembourg	0	0	0	0	0	0	0	0	0	0
Malta	0	0	0	0	0	0	0	0	0	0
The Netherlands	0	0	0	0	0	2	1	1	1	5
Norway	0	0	0	1	0	1	0	0	2	4
Poland	NA	NA	NA	NA	NA	NA	2	0	0	2
Portugal[b]	NA	NA	NA	NA	NA	NA	NA	0	0	0
Romania	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Slovakia	0	0	0	0	0	0	0	0	0	0
Slovenia	0	0	0	0	0	0	0	0	0	0
Spain	0	0	0	155	266	230	135	260	331	1,377
Sweden	0	0	0	0	0	0	0	1	1	2
EU/EEA	0	0	4	158	272	236	152	335	655	1,812

EEA: European Economic Area; EU: European Union; NA: information not available at national level.
[a] France reported one case retrospectively identified in 2007 which is not included in this table [18].
[b] Portugal reported one C. auris case for 2022 which is not included in this table.
Cells including one or more cases are coloured in grey for better visibility

Complications of Treating *Candida auris*

- Survive industrial-strength cleaning on hospital room surfaces and equipment.
- Diversity infections including ear infections, bloodstream infections, and wound infections.
- Drug resistance and limited antifungals.
- The public health agency should treat the *C. auris* outbreak with the same degree of urgency as the 2014 Ebola outbreak.
- “It [*C. auris*] can be everywhere; it can be on anything. Hospitals may have to rip out their ceilings and walls to have it removed.

Fungal infections- Superficial mycosis

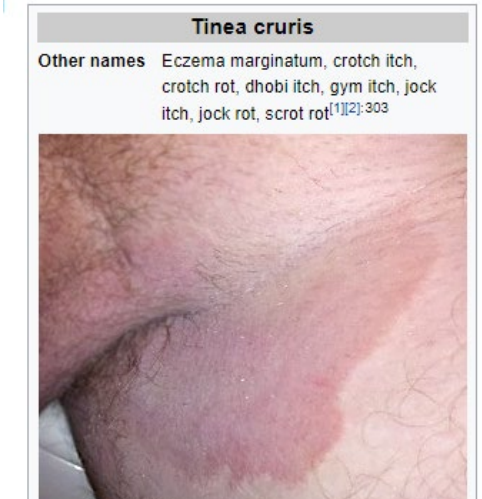
- Dermatophytosis, also known as ringworm, is a fungal infection of the skin, nail
- Superficial mycosis: onychomycosis,

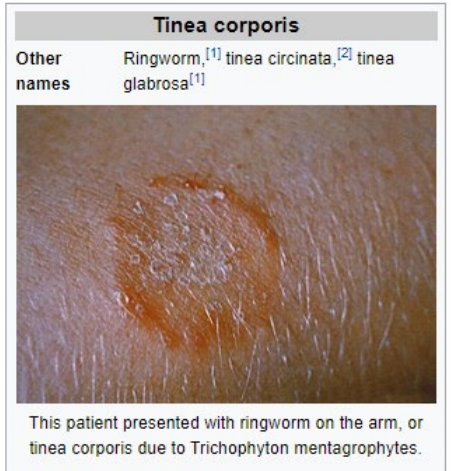
tinea pedis, tinea manus, tinea cruris or tinea corporis

Tinea unguium

Tinea pedis

Tinea manuum



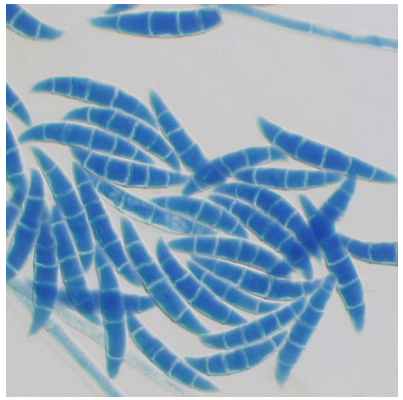


Onychomycosis

Symptoms: white or yellow nail discoloration, thickening of the nail, and separation of the nail from the nail bed. Toenails or fingernails may be affected, but it is more common for toenails.

Causative: dermatophytes and *Fusarium*

Dermatophytes

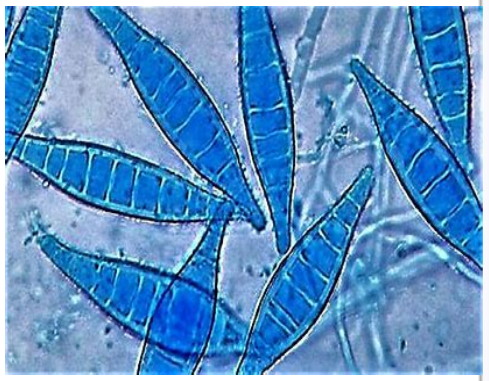


Fusarium

Athlete's foot, (***tinea pedis)***

Symptoms: itching, scaling, cracking and redness.

Causative: **Trichophyton, Epidermophyton, and Microsporum**



Athlete's foot

Other names	Tinea pedis, ringworm of the foot,[1] moccasin foot[2]

A severe case of athlete's foot.

Risk group: People with diabetes or weakened immune system are more susceptible to the disease. Risk factor sweating increases the risk of infection and makes treatment more difficult

Tinea manuum

Symptoms : diffuse scaling on the palms or back of hands
Itchy

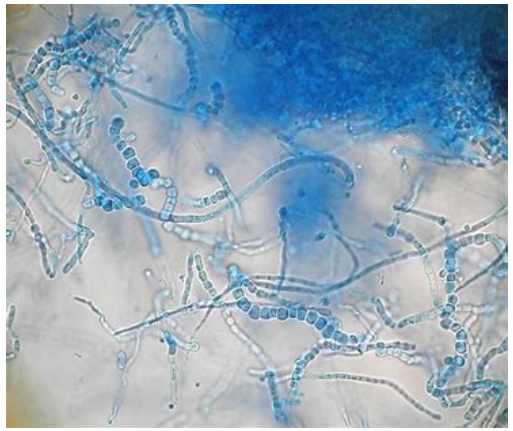
Causative: *Trichophyton rubrum*

Risk factors: Diabetes, high blood pressure, weak immune system, humid surroundings, excessive sweating, recurrent hand trauma and cracks in feet are for tinea manuum.
Risk group: Pet owners and farmworkers are also at higher risk.

Tinea cruris (**Jock itch**),

Symptoms: an intensely itchy red raised rash with a scaly well-defined curved border. It is often associated with athletes foot and fungal nail infections, excessive sweating and sharing of infected towels or sports clothing. It is uncommon in children.

The type of fungus involved may vary in different parts of the world; for example, *Trichophyton rubrum* and *Epidermophyton floccosum* are common in New Zealand. Less commonly *Trichophyton mentagrophytes* and *Trichophyton verrucosum* are involved. *Trichophyton interdigitale* has also been implicated.



Tinea corporis
Symptoms: arms and legs, especially on glabrous skin

Causative: dermatophyte

These tiny organisms normally live on the superficial skin surface, and when the opportunity is right, they can induce a rash or infection.[5]

Dermatophyte

Tinea corporis

Other names	Ringworm,[1] tinea circinata,[2] tinea glabrosa[1]

This patient presented with ringworm on the arm, or tinea corporis due to Trichophyton mentagrophytes.

Specialty	Dermatology

Treatments

- local and systemic.
- Local antifungals--topically or vaginally
- Systemic antifungals----orally or intravenously.
- Systemically include ketoconazole, itraconazole, fluconazole, fosfluconazole, voriconazole, posaconazole, and isavuconazole.griseofulvin and terbinafine.

In a lot of countries, Terbinafine is the first-line treatment

Alarming India-wide phenomenon of antifungal resistance in dermatophytes: A multicentre study

Andreas Ebert, Michel Monod, Karine Salamin, Anke Burmester, Silke Uhrlaß, Cornelia Wiegand, Uta-Christina Hipler, Constanze Krüger, Daniela Koch, Franziska Wittig, Shyam B. Verma, Archana Singal, Sanjeev Gupta, Resham Vasani, Abir Saraswat, Rengarajan Madhu, Saumya Panda, Anupam Das, Mahendra M. Kura, Akshy Kumar, Shital Poojary, Sibylle Schirm, Yvonne Gräser, Uwe Paasch, Pietro Nenoff ... See fewer authors

First published: 16 April 2020 | https://doi.org/10.1111/myc.13091 | Citations: 60

India

India

⇨ 71% resistance to terbinafine

Journal of *Fungi* MDPI

Article

Terbinafine Resistance in Dermatophytes: A French Multicenter Prospective Study

Alicia Moreno-Sabater [1,2,*], Anne-Cécile Normand [3], Anne-Laure Bidaud [4], Geneviève Cremer [5], Françoise Foulet [6,7], Sophie Brun [8,9], Christine Bonnal [10], Nawel Aït-Ammar [6,7], Arnaud Jabet [1,3], Aymen Ayachi [10], Renaud Piarroux [3,11], Françoise Botterel [6,7], Sandrine Houzé [10,12], Guillaume Desoubeaux [13], Christophe Hennequin [1,14] and Eric Dannaoui [4,7,15,*]

France

⇨ 0.5% resistance to terbinafine---57% in another hospital centre

Eur J Clin Microbiol Infect Dis. 2018 Oct;37(10):1841-1846. doi: 10.1007/s10096-018-3317-4. Epub 2018 Jul 7.

Antifungal drug susceptibility profile of clinically important dermatophytes and determination of point mutations in terbinafine-resistant isolates

Zahra Salehi [1], Masoomeh Shams-Ghahfarokhi [2], Mehdi Razzaghi-Abyaneh [3]

Affiliations – collapse

Affiliations

1 Department of Mycology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, 14115-331, Iran.
2 Department of Mycology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, 14115-331, Iran. shamsm@modares.ac.ir.
3 Department of Mycology, Pasteur Institute of Iran, Tehran, 13164, Iran.

Iran → 2.75% resistance to terbinafine

Open Access Article

Increasing Terbinafine Resistance in Danish *Trichophyton* Isolates 2019–2020

by Karen Marie Thyssen Astvad [1,*], Rasmus Krøger Hare [1], Karin Meinike Jørgensen [1], Ditte Marie Lindhardt Saunte [1,2,3], Philip Kjettinge Thomsen [4] and Maiken Cavling Arendrup [1,3,5]

1 Unit of Mycology, Statens Serum Institut, DK-2300 Copenhagen, Denmark
2 Department of Dermatology, Zealand University Hospital, DK-4000 Roskilde, Denmark
3 Department of Clinical Medicine, Faculty of Health Science, University of Copenhagen, DK-2100 Copenhagen, Denmark
4 Department of Clinical Microbiology, Aalborg University Hospital, DK-9220 Aalborg, Denmark
5 Department of Clinical Microbiology, Rigshospitalet, DK-2100 Copenhagen, Denmark
* Author to whom correspondence should be addressed.

Denmark → >0.1% resistance to terbinafine

J Eur Acad Dermatol Venereol. 2021 Apr;35(4):1017-1025. doi: 10.1111/jdv.17106. Epub 2021 Feb 3.

Epidemiological and clinical aspects of Trichophyton mentagrophytes/Trichophyton interdigitale infections in the Zurich area: a retrospective study using genotyping

M Klinger [1 2], M Theiler [3], P P Bosshard [1 2]

Affiliations – collapse

Affiliations

1 Department of Dermatology, University Hospital Zurich, Zurich, Switzerland.
2 Faculty of Medicine, University of Zurich, Zurich, Switzerland.
3 Pediatric Skin Center, Dermatology Department, University Children's Hospital Zurich, Zürich, Switzerland.

Switzerland

⇨ 2.4% resistance to terbinafine

J Cutan Med Surg. 2022 Jul-Aug;26(4):371-376. doi: 10.1177/12034754221077891. Epub 2022 Feb 10.

Terbinafine Resistant *Trichophyton Indotineae* Isolated in Patients With Superficial Dermatophyte Infection in Canadian Patients

Claudia J Posso-De Los Rios [1], Enas Tadros [1], Richard C Summerbell [2 3 4], James A Scott [2 3 4]

Affiliations – collapse

Affiliations

1 Dermatology Clinic, DermCare. 1065 Canadian Pl Unit 206, Mississauga, ON, Canada.
2 7938274071 Dalla Lana School of Public Health, University of Toronto, ON, Canada.
3 Dynacare Laboratories. 115 Midair Court, Brampton, ON, Canada.
4 Sporometrics, 219 Dufferin Street, Suite 20C, Toronto, ON, Canada.

Canada

⇨ 100% resistance to terbinafine

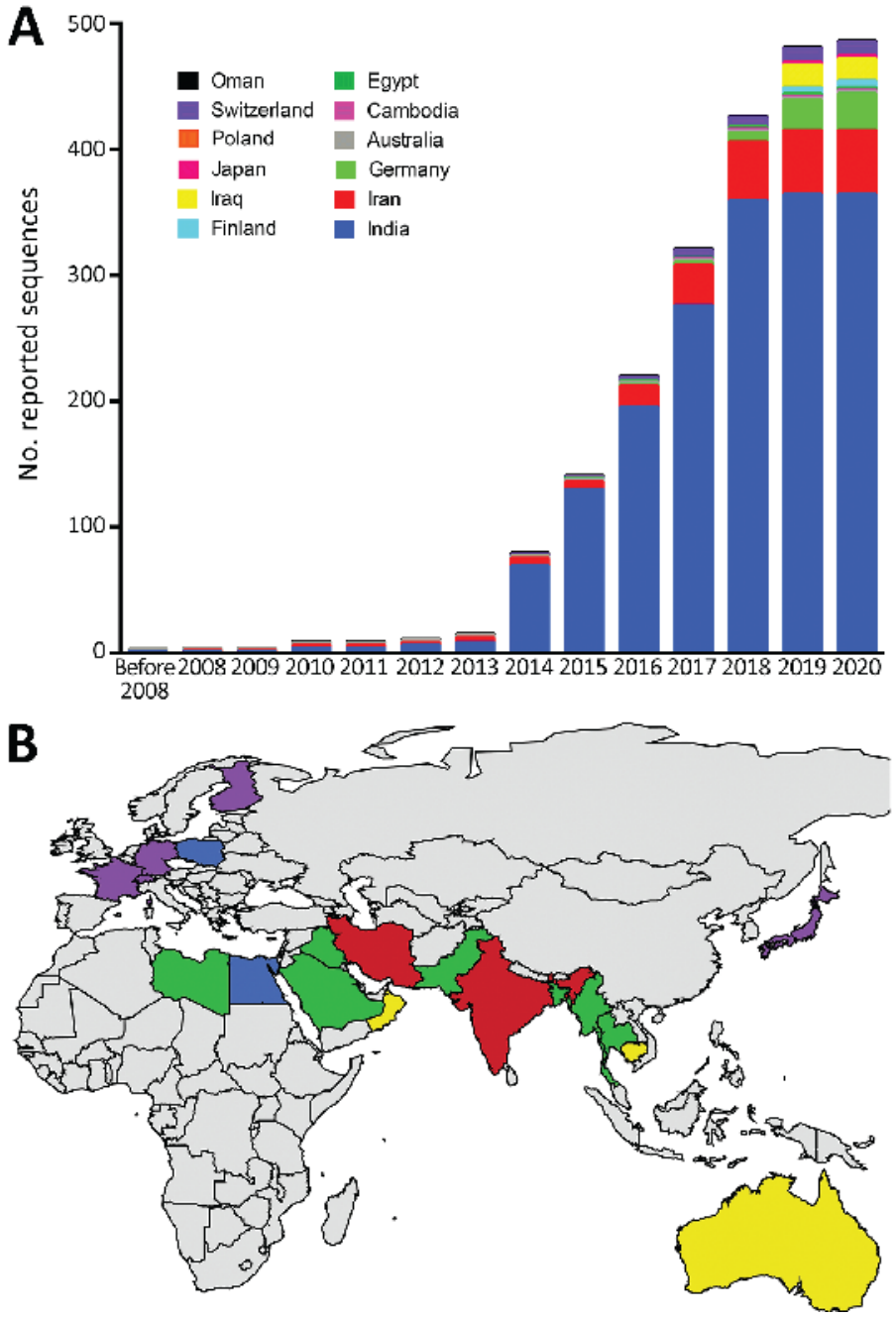


Figure 1. Analysis of dynamic and geographic distribution of *Trichophyton indotineae* reported sequences from France (this study) and reference sequences from GenBank for 2004–2021 A) Cumulative curves of 486 published sequences; B) geographic distribution of 537 published sequences. Red, countries with reported endemic cases; purple, countries with imported cases (but rare cases of endemic transmission cannot be ruled out); green, probable country sources of imported cases; yellow, countries with reported sporadic human cases without additional available information (also identified in Poland); blue, countries with *T. indotineae* sequences reported in animal infections (also reported in India). World map was created using JMP Pro 15.2.0 (https://www.jmp.com). For internal transcribed spacer sequence-based screening, we retrieved ITS1-5.8S-ITS2 sequences *T. interdigitale, T. mentagrophytes, T. indotineae* and also *Arthroderma benhamiae, A. simii, A. vanbreuseghemii, T. benhamiae, T. bullosum, T. concentricum, T. equinum, T. erinacei, T. quinckeanum, T. simii, T. schoenleinii, T. tonsurans*, and *T. verrucosum*. For sequences matching *T. indotineae* (internal transcribed spacer reference sequence JN133999), we searched associated literature on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc).

Resistance mechanism underpin the Terbinafine resistance in dermatophyte.

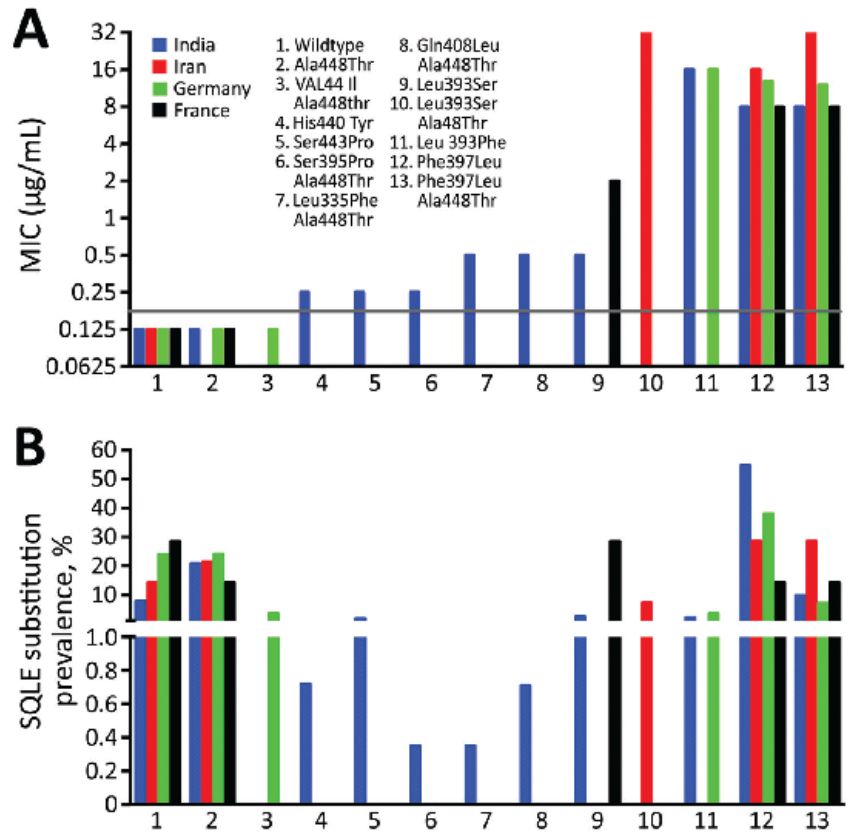


Figure 2. *Trichophyton indotineae* susceptibility to terbinafine reported from 4 countries. A) Relationships between terbinafine MIC and codon changes reported in isolates from different countries. Grey line shows terbinafine susceptibility threshold of 0.2 µg/mL. Available MICs were determined using the Clinical Laboratory and Standards Institute (https://clsi.org) or EUCAST (https://eucast.org) methods. Data show mean values. B) Prevalence of substitution points in the gene encoding SQLE. Sources shown in the Appendix (https://wwwnc.cdc.gov/EID/article/28/1/21-0883-App1.pdf). SQLE, squalene epoxidase enzyme.

Fusarium associated infection

1. ‘Superficial’ atypical Infections

2. Keratitis

3. Deep infections

4. Spreading infections

Fusarium associated infection

1. ‘Superficial’ atypical Infections

2. Keratitis

3. Deep infections

4. Disseminated infections

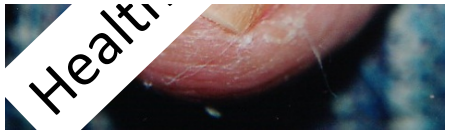
Fusarium associated infection

1. ‘Superficial’ atypical Infections

1 %

1 %

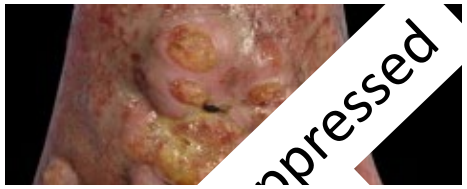
low



2. Keratitis

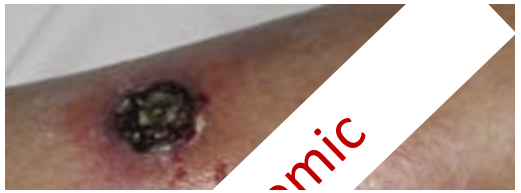
250.000/year

3. Deep infections



???

4. Disseminated infections



1000(s)/year

Antifungal resistance in *Fusarium*

Range of antifungal susceptibility MIC (µg/ml)		Allylamine → squalene epoxidase	Azoles → lanosterol 14-alpha-demethylase									Polyenes → ergosterol		Echinocandins → glucan synthesis			Pyramidine anal. → RNA	Phenol ether →ubiquitine?
Species	SC	TBF	ABC	FLZ	ISA	ITZ	KTZ	MCZ	PSZ	RVZ	VRZ	AMB	NAT	ANF	CSP	MFG	5FC	PNT
F. solani	FSSC	>16		>64	8-16	>16	>88	>64	>16		1-32	0.5-8	2-8	>16	>16	8-256	>128	8-32
F. falciforme	FSSC	1-2		>128		>8->32	>32	>16	>8		4	0.5-4	4	>16	16	>16	>64-256	
F. keratoplasticum	FSSC			>64		>64			0.12-16		8	2		>16	>16		>64	
F. lichenicola	FSSC	>2		>64		>8-100		>16	>8		1.56-8	0.25-4	4	>16	>16	>16	>64	
F. petroliphilum	FSSC			>64	>16	>16			>16		8-16	0.5-1		>16	>16	>8	>64	
F. solani s.s.	FSSC			>64		>16			>16		2-8	0.25-1		>16	>16		>64	
haplotype-6	FSSC			>64		>16					2	2		>16	>16		>64	
F. oxysporum	FOSC	0.25-32				1-20	33	72	0.16-16		2-16	0.12-4		>16	16		>64	
F. dimerum	FDSC	0.12-2	4-16	>80		16-32	1-32	>40	>16	4-16	2-8	0.4-2		>16	>16		>320	
F. delphinoides	FDSC																	
F. chlamydosporum	FCSC	0.125-1	4-32			2	3.2-		0.5-32	1-16	1-4	0.8-6					>100	
F. incarnatum	FIESC	0.5-32	8-32	>80		>10-32	2->50	>40	1-32	8-16	2-4	0.5-8					>320	
F. equiseti	FIESC	4-16				16			2	16	4	0.5-1						
F. sporotrichioides	FSAMSC										>16	4						
F. acutatum	FFSC			>64	4->16	>16			1-2		2-8	1-8	4			>8		
F. ananatum	FFSC			>64	1-8	>16			0.5-1		1-4	0.125–	4			>8		
F. anthophilum	FFSC			>64	1-8	>16			0.25-		1-4	0.25-1	4			>8		
F. andiyazi	FFSC			16->64	1-8	8->16			1		2	8	4	8	16	>8		
F. fujikuroi	FFSC			>64	4-16	16->64			1-2		2-8	0.25–1	4			>8		
F. napiforme	FFSC	0.06-	4	>64	2-8	>16	8-32	32	32	2-4	1-4	1-8	4			>8	256	
F. nygamai	FFSC	0.125-2	8-16	>64	8->16	32	16-32		32	4-16	4-8	2-8	4			>8		
F. polyphialidicum	FFSC			>64														
F. proliferatum	FFSC	0.1-32	8-16	>64	4->16	16-32	8-32		2-32	8-32	4-16	1-8	4	>16	>16	>8	>64	
F. sacchari	FFSC	0.125-	4-8	64	2-16	16-32	2-32	16	2	4-8	2-4	1-2	4			>8	128	
F. subglutinans	FFSC			>64	2-4	>16			0.125–		1-2	0.5-4	4			>8		
F. temperatum	FFSC			>64	2-4	>16			0.25		1	0.5	4	4-8		>8		
F. thapsinum	FFSC	0.25-0.5	2-16	>64	8-16	>16	>16		2->16	8->16	1-4	1-4	4			>8		
F. verticillioides	FFSC	0.1-32		>64	1-2	1->16			0.25-		1-16	0.5-4	4	>16	>16	>8	>64	

Netherlands ------ no surveillance data

Fungal infections among nursing home residents

Objective and research questions

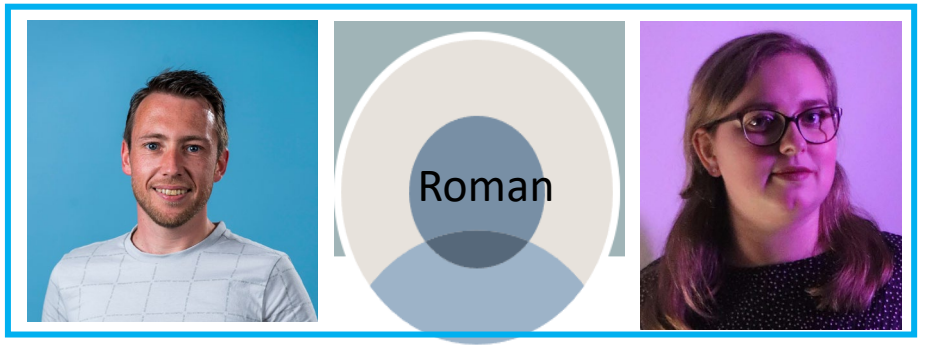
Therefore, the aim of this study is to investigate the epidemiology of fungal skin infections and toe infection in nursing home residents in the Netherlands.

The main research questions that will be studied are:

- What is the prevalence of fungal skin infections (dermatophytosis) and toenail fungal infection (onychomycosis) in residents of Dutch nursing homes?
- Which fungal species cause these infection in Dutch nursing homes?
- What are the antifungal resistance profile of these causal fungi, is there any correlation between resistance and the usage of antifungals in residents of Dutch nursing homes?
- What is the resistance mechanism of these resistant isolates?
- whether there is an epidemiological link with the Indian subcontinent or other European countries.

RIVM - Mycology Team

❖ Mycology Teams (MT&Knowledge&Skill)

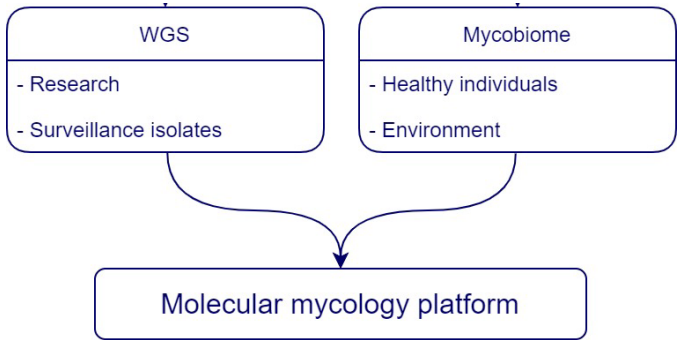


A Phd Candidate wanted

❖ Mycology Web/Refer Lab S0.05 (Hard drive)

❖ Surveillance and Relevant Research (Application)

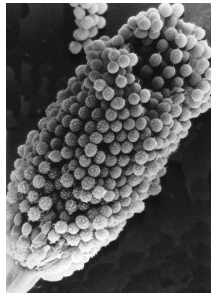
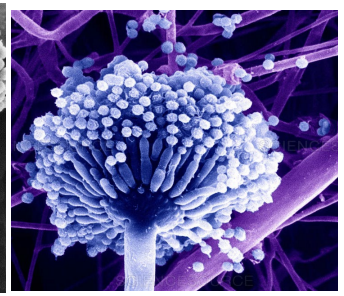
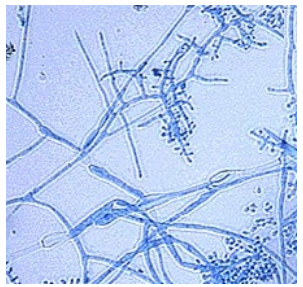
❖ Molecular mycology platform (Software)



Mycology teams' scope

Resistance in fungi

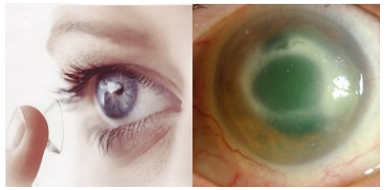
- Be aware of upcoming fungal pathognes (*Aspergillus fumigatus*/ *A. niger* complex/ *Trichophyton indotineae*)
- Finding hotspots– ---prevention

One Public Health

Mycobiome and Dysbiosis

Fusarium Eye infection



Candida infection




Preparedness & Response

Candida auris

Transmission routes

Water, Air and Birds, Animals???



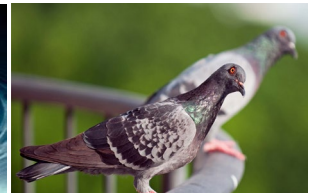



Image resource: WIKI

Contacts:
Thijs Bosch <Thijs.bosch@rivm.nl>
Julia Zhang <Julia.zhang@rivm.nl>

World Health Organization

WHO fungal priority pathogens list to guide research, development and public health action

Oct-2022

Table 3. WHO fungal priority pathogens list

Critical group	High group	Medium group
Cryptococcus neoformans	*Nakaseomyces glabrata (Candida glabrata)*	*Scedosporium* spp.
Candida auris	*Histoplasma* spp.	*Lomentospora prolificans*
Aspergillus fumigatus	Eumycetoma causative agents	*Coccidioides* spp.
Candida albicans	Mucorales	*Pichia kudriavzeveii (Candida krusei)*
	Fusarium spp.	*Cryptococcus gattii*
	Candida tropicalis	*Talaromyces marneffei*
	Candida parapsilosis	*Pneumocystis jirovecii*
		Paracoccidioides spp.

AMR
Tackling Antimicrobial Resistance