Fungal Diversity
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The world's ten most feared fungi

Kevin D. Hyde[1,2] · Abdullah M. S. Al-Hatmi[3,6] · Birgitte Andersen[4] · Teun Boekhout[5,6] · Walter Buzina[7] · Thomas L. Dawson Jr.[8,9] · Dan C. Eastwood[10] · E. B. Gareth Jones[12] · Sybren de Hoog[6,11] · Yingqian Kang[13] · Joyce E. Longcore[14] · Eric H. C. McKenzie[15] · Jacques F. Meis[11,16] · Laetitia Pinson-Gadais[17] · Achala R. Rathnayaka[2] · Florence Richard-Forget[17] · Marc Stadler[18] · Bart Theelen[6] · Benjarong Thongbai[18] · Clement K. M. Tsui[19,20]

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Abstract
An account is provided of the world's ten most feared fungi. Within areas of interest, we have organized the entries in the order of concern. We put four human pathogens first as this is of concern to most people. This is followed by fungi producing mycotoxins that are highly harmful for humans; *Aspergillus flavus*, the main producer of aflatoxins, was used as an example. Problems due to indoor air fungi may also directly affect our health and we use *Stachybotrys chartarum* as an example. Not everyone collects and eats edible mushrooms. However, fatalities caused by mushroom intoxications often make news headlines and therefore we include one of the most poisonous of all mushrooms, *Amanita phalloides*, as an example. We then move on to the fungi that damage our dwellings causing serious anxiety by rotting our timber structures and flooring. *Serpula lacrymans*, which causes dry rot is an excellent example. The next example serves to represent all plant and forest pathogens. Here we chose *Austropuccinia psidii* as it is causing devastating effects in Australia and will probably do likewise in New Zealand. Finally, we chose an important amphibian pathogen which is causing serious declines in the numbers of frogs and other amphibians worldwide. Although we target the top ten most feared fungi, numerous others are causing serious concern to human health, plant production, forestry, other animals and our factories and dwellings. By highlighting ten feared fungi as an example, we aim to promote public awareness of the cost and importance of fungi.

Keywords Aflatoxicosis · Batrachochytrium · *Candida auris* · Frog decline · Poisonous fungi · Human pathogens · Indoor fungi · Forest pathogens · Wood decay

Introduction

Although fungi are essential for life on earth because of their role in nutrient cycling, and their present and potential uses in biotechnology, they also cause severe problems in many aspects of life. Some of these problems are obvious to the public and well-publicized (bread mould, poisonous mushrooms, rot of timber in houses, human pathogens), while others are equally hazardous, but less well-known to the public (indoor air fungi, mycotoxin producers, hospital outbreaks). We review what we consider to be the top ten most feared fungal species. In considering these, we bring together both well-publicized, as well as less well-known species that cause huge problems and should essentially be feared. The inclusion of species in this paper is based on fear and their cost and importance to the public. We have been rational in our approach by choosing individual species (e.g., *Stachybotrys chartarum* is used to represent indoor air fungi and *Austropuccinia psidii* to represent plant and forest disease.).

Although in this paper we stress the detrimental fungi, it must also be recognized that fungi also play a huge positive role in our everyday lives. Fungi are prominent decomposers of dead plant materials (Mortimer et al. 2012). They secrete enzymes into the environment and the substrates they inhabit, increasing the nutrients available for living plants and are essential for nutrient cycling (Lange et al.

✉ Kevin D. Hyde
kdhyde3@gmail.com

Walter Buzina
walter.buzina@medunigraz.at

Extended author information available on the last page of the article

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2012). Also, mycorrhizal fungi can provide essential nutrients for crops, shrubs and trees (Mortimer et al. 2012) and increase their growth and protect them from various stresses. In the food and beverage industries fungi are essential for the production of cheeses, bread and beverages such as wines and spirits (Lange 2014) and are used as food supplements. Mushrooms themselves are an important widely consumed food source, and in China several species are highly prized and valuable (Mortimer et al. 2012). They are important providers of medicines such as penicillin, cyclosporin and lovastatin, are commonly used in the cosmetic industry and are a treasure trove of novel compounds (Hyde et al. 2010a, b; Da Silva et al. 2012a, b, 2013; Bills and Gloer 2016; Karwehl and Stadler 2017).

In this paper we provide synopses for what we consider to be the ten most feared fungi. Each provides background knowledge on both the organism and problems it causes. Reasons as to why the species should be feared are given. We discuss the present situation with future predictions and where possible, give details of ongoing research and possible future research direction. It is hoped that by highlighting the ten most feared fungi, we can promote public awareness of the cost and importance of fungi in general. We also provide background teaching material for University lecturers and school teachers so that they can make students more aware of the importance of fungi.

We have organized the entries in the order of perceived concern by the authors. There are numerous other fungi that should be feared and are causing serious concern to human health, plant production, forestry, other animals and our factories and dwellings.

Human disease

Fungi causing infection are particularly alarming. Fungal infections are often chronic and difficult to treat. Some, after a long and painful disease process, are horribly mutilating, and may lead to death. Luckily, of the millions of fungal species, only a small fraction are able to cause any disorder. Since the first discovery of fungal infection in 1842, and despite the growing susceptible populations of patients suffering from immune disorders and diabetes, only about 650 species have been reported to cause infection (de Hoog et al. 2018). Excluding the opportunistic pathogens that only occasionally cause infections in severely immunocompromized patients, the list of species recurrently infecting humans is even smaller. Only about 150 species are relatively common.

Broadly, three categories can be distinguished: (1) pathogens, i.e. species that have an advantage of higher fitness if a vertebrate is used in any stage of their lifecycle; (2) opportunists, i.e. species that occupy environmental habitats where they have characteristics that coincidentally enhance tissue invasion if they are accidentally introduced into a human body, and (3) colonizers, which are dependent on products of the human body, normally without becoming invasive. It may seem somewhat counter-intuitive, but healthy individuals have more to fear from opportunists than from pathogens. Our acquired cellular immunity effectively controls infection by pathogens. Consequently, infections by pathogens in healthy individuals are mostly asymptomatic or only lead to mild infection. Diseases caused by severe pathogens are typically associated with dysfunction of the acquired immune system, and therefore such infections are commonly associated with AIDS or cancer chemotherapy. The immune system is, however, naive towards most opportunists. Even in hosts with a functional immune system, these infections can cause severe morbidity. The host response may be inappropriate, leading to a chronic, slowly aggravating infection. This usually occurs after traumatic inoculation through the skin, resulting in deformations as in chromoblastomycosis or mycetoma. If inhaled, the opportunist may accidentally reach the blood, and then systemic or disseminated infection may occur, which ultimately leads to death. Fatal infections in otherwise healthy individuals thus are often caused by opportunists rather than by pathogens.

Pathogens are nearly limited to a single order, the Onygenales, containing dermatophytes (*Trichophyton* and allies) and the systemic dimorphic fungi (*Coccidioides, Histoplasma*, and relatives). Many species of both groups have a natural life cycle in association with wild animals such as bats or rodents. The phylogeny of dermatophytes broadly reflects a consistent pattern of evolution towards increasing adaptation to mammal hosts (de Hoog et al. 2017). Natural host animals often do not seem to suffer from the infection (Hubálek et al. 1995); even abundant pulmonary presence of adiaspores often looks more like colonization rather than pathogenicity. Some single species or species groups outside the Onygenales, such as *Cryptococcus gattii,* the *C. neoformans* species complex (Filobasidiales) and *Talaromyces marneffei* (Eurotiales), show a similar behaviour but are enigmatic in that no obvious phylogenetic origin of their pathogenicity is known. Such species, similar to onygenalean taxa, cause serious mortality among HIV-positive populations in endemic areas, but are rarely a threat to immunocompetent individuals.

Several opportunistic fungi are, however, able to cause fatal disease in apparently healthy persons. Such species are therefore listed among the most dangerous fungi, being attributed to the BioSafety Level 3 category (de Hoog et al. 2018). One of these is *Cladophialophora bantiana*, which although very rare, is dangerous because it is almost exclusively known from human infections, mostly of the brain, causing potentially fatal disease in otherwise healthy individuals. This fungus is chosen as number one of the

World's most feared fungi. Even with treatment the death rate is still close to 60% (Kantarcioglu and de Hoog 2004). *Candida auris* is an enigmatic yeast that in the past decade has emerged in hospital outbreaks. Its high degree of multi drug-resistance makes this fungus a significant public health problem and is chosen number three of the World's most feared fungi. *Talaromyces marneffei* causes an AIDS-associated illness, but recently the fungus even emerged in populations without known immune disorder. We still do not understand why suddenly healthy patients are also at risk and this species is therefore chosen as number two of the worlds most feared fungi. The fourth most feared human associated pathogenic fungus is *Malassezia globosa,* the "dandruff fungus". Although not a serious pathogen, it has undesirable consequences that most of us fear.

1. Cladophialophora bantiana: the brain-eating fungus

Cladophialophora bantiana is a filamentous fungus classified in the order Chaetothyriales among species that are often referred to as 'black yeasts'. This term refers to the budding cells of the best-known genus of the order, *Exophiala*. The Chaetothyriales are ecologically remarkable, as members of this order can be found in very different environments, but not in habitats that are commonly colonized by other microbes, such as soil or plant debris. A general hypothesis to explain this vicarious occurrence is the assumption that they are weak competitors against rapidly growing molds such as *Aspergillus* and *Fusarium* species. Black yeast-like fungi survive at the extreme, be it cold, hot, nutrient-poor, toxic, or a combination of those.

Quite a few species in the order are known only from human-made habitats, such as steam baths, toxic waste, creosoted oak-wood, oil-polluted soil, industrial exhaust, and garages. In the large, phylogenetically derived family Herpotrichiellaceae, numerous species have been reported from infections in vertebrate hosts. Remarkably, the main host is *Homo-sapiens*, in addition to a wide diversity of cold-blooded, waterborne animals such as fish, frogs and toads—with hardly any host in between. De Hoog et al. (2011) suggested that this might be explained by the moist skin that is common to all these hosts, whereas non-infected animals have a thick, water-repellent cover of feathers or fur. Some suggested virulence factors of melanin and muriform cells may also respond in an illogical way (Song et al. 2017) and do not seem to be protective when they are needed, underlining an opportunistic character. Members of Herpotrichiellaceae are quite remarkable in their preference of extreme conditions and ability to cause infection. Prenafeta-Boldú et al. (2006) referred to this as 'dual ecology' of the group, species being found causing human infection and in sites rich in toxic hydrocarbons. *Exophiala dermatitidis* is a striking example of this behaviour, commonly being encountered in garages and fuel (Isola et al. 2013) and as a systemic invader of otherwise apparently healthy humans.

Is Cladophialophora bantiana neurotropic?

The order Chaetothyriales contains a remarkably high number of species of primary neurotropic disease. Two species almost exclusively cause this clinical syndrome: *Cladophialophora bantiana* and *Rhinocladiella mackenziei* (Moreno et al. 2018). Primary brain infection occurs without any known prior history of disease and without obvious portal of entry (Horré and de Hoog 1999). The disease mostly has an unremarkable anamnesis (the case history of a medical patient as recalled by the patient): early clinical symptoms may remain absent and often consultation of a physician is not sought. Severe neurological symptoms, such as severe headache, unilateral paralysis, confusion or slurred speech become apparent unexpectedly (Ahmad et al. 2017), when the infection is already in an advanced stage. Patients also may get seizures, often have nausea and vomiting, and occasionally have problems with vision eventually leading to blindness. Some cases of hydrocephalus have also been reported (Garg et al. 2007). Patients usually are alert upon admission, despite aggravating clinical symptoms. The disease may occur in immunocompromised patients (and if so, then it mostly affects individuals under prolonged corticosteroid therapy) but is more often observed in otherwise apparently healthy people (Kantarcioglu and de Hoog 2004).

Without appropriate therapy the infection is almost invariably fatal, and even with combined surgery and antifungal therapy the mortality in immunocompetent patients is still among the highest death rates among the diseases caused by fungal pathogens (Chakrabarti et al. 2016). Due to their low penetration into cerebral tissue, most commonly used antimycotic drugs have limited effectivity (Garzoni et al. 2008). Several hundreds of cases of this disease have been published worldwide and particularly in India (Garg et al. 2007).

Why Cladophialophora bantiana should be feared

Cladophialophora bantiana (and its older synonyms *Cladosporium bantianum* and *Xylohypha bantiana*) yielded 33,490 Google hits (per 18-06-2018). This does not indicate large public interest. However, this fungus is almost exclusively recorded in the otherwise healthy human brain, while its natural niche is unknown, and this is worrying (Fig. 1). Very few environmental strains of this species have so far been reported. Confirmed environmental strains were from saw dust and house dust (http://www.westerdijkinstitute.nl/). Kantarcioglu et al. (2016) reported a case of a coal miner who was previously hit by coal rocks. This possibly indicates a hyper-dry or osmotic natural habitat, similar to *Rhinocladiella mackenziei*. Inhalation via dry

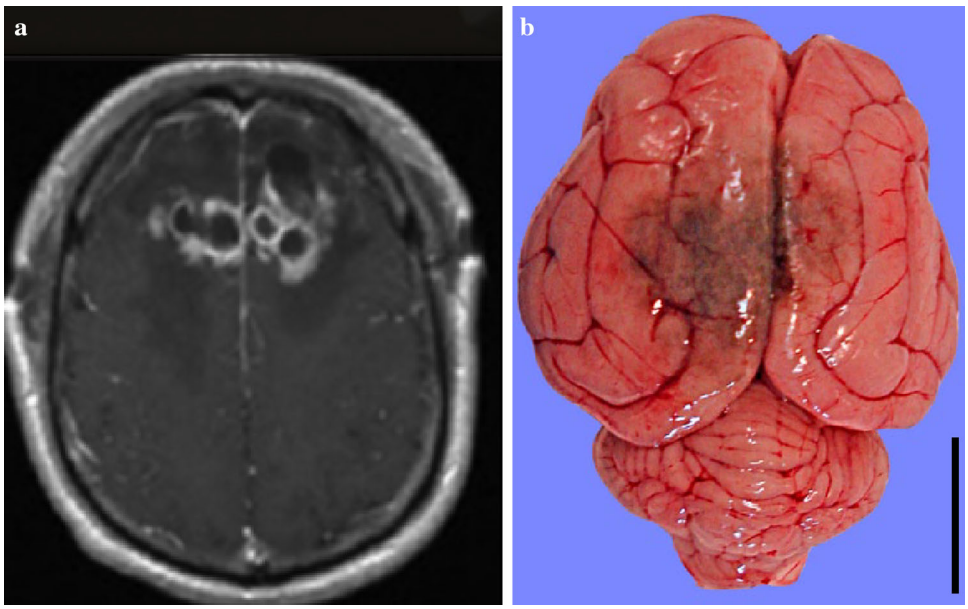

Fig. 1 **a** Cerebral abscess caused by *Cladophialophora bantiana* in an individual with controlled diabetes. Taken with permission of the authors from Aljuboori et al. (2017). **b** Cerebral *C. bantiana* infection in cat brain showing brown area of fungal infection and swollen gyri, particularly at the left side. Bar 1.5 cm. Taken with permission of the authors from Russell et al. (2016)

particles after airborne dispersal could then be the main route of infection. The conidia of *Cladophialophora bantiana* are hydrophobic, but are released reluctantly, and thus airborne dispersal is unlikely to be efficient. Possibly localized airborne dispersal is comparable to that observed in *Talaromyces marneffei* (Fisher et al. 2005). However, this fungus is restricted to Southeast Asia, while *Cladophialophora bantiana* has a global prevalence.

Systemic infections by *C. bantiana* have a long and symptomless incubation period. Hussey et al. (2005) reported a case of nodules becoming sudden and severe 17 years after implantation of a wooden splinter. Once the disease becomes apparent in the brain, where immune responses are moderate, the patient develops severe symptoms and may be approaching death.

Coccidioides immitis has been on the US List of Select Agents containing organisms that potentially could be used for terrorism or biological warfare, but was removed (American Society for Microbiology (2010) https://www.asm.org/index.php/component/content/article?id=2570. Accessed August 2018) because of its widespread occurrence in nature and concomitant frequent asymptomatic infections among healthy patient populations. For *Cladophialophora bantiana*, we can only speculate about source and route of infection. The almost exclusive occurrence in the human brain would suggest that this is the natural habitat of the fungus, however this is however unlikely. Opportunistic members of Chaetothyriales are commonly found in human-made, toxic hydrocarbon-rich environments, among which are creosoted wood (Gümral et al. 2014), biofilters for cleaning of toxic industrial exhaust (Cox et al. 1996) or polluted mines (Seyedmousavi et al. 2011). The supposed isolation of a *Cladophialophora* species from such filters once necessitated deep health analysis of employees of a biofilter company in The Netherlands and, despite absence of infection, led to a halt of this type of research by the company. Later, with the aid of more advanced diagnostic methods, it was found that the fungus of concern was not *C. bantiana* but a non-virulent molecular sibling, *C. psammophila* (Badali et al. 2011). The example of the Dutch company has shown that isolation of this type of fungus from an environment considered conducive to its development, is cause for concern especially until diagnosis is undertaken. During the long incubation period the employees constantly worried that they suddenly might develop this potentially fatal disease. Thus the threat of infection is the main problem. It remains disturbing that in the absence of a known environmental habitat no public health measures can be taken to decrease the risk of infection. It is noteworthy to record that primary brain infection, in contrast to cutaneous chromoblastomycosis among rural populations by other members of Chaetothyriales, is a problem of urban populations.

Recent research efforts

Sequenced genomes of "black yeasts" (Teixeira et al. 2017) may shed light upon the biology and ecology of *Cladophialophora bantiana*. The equally neurotropic relative *Rhinocladiella mackenziei* was recently found to possess choline and trehalose pathways, and expanded alcohol and aldehyde dehydrogenases, all of which indicate the potential of the fungus to survive under extreme conditions, and showed expansion of cytochromes P450 with the presence of several pathways to degrade toxic monoaromatic hydrocarbons (Moreno et al. 2018). It was therefore speculated that *R. mackenziei* might have its

natural habitat in the oil-polluted desert rather than in the human brain. Genomic similarity with *Cladophialophora bantiana* makes its possible association with dry dust and hydrocarbon pollution more probable. While *Rhinocladiella mackenziei* is endemic to the Middle East, *Cladophialophora bantiana* might expand with increasing hydrocarbon-based pollution of the urban environment.

Conclusions

The main problem with *Cladophialophora bantiana* is the lack of basic knowledge of the biology of this fungus. At this moment we only know the negative side of the fungus as a severe brain-infecting agent. It however, appears to be common in a yet undetermined environmental niche, which was also the case with *Exophiala dermatitidis*, initially only known from fatal dissemination in East Asia (Hiruma et al. 1993). It is now also known to be very common in human-made in and outdoor environments, however, the likely levels of daily exposure means the chance of infection is extremely low. It is possible that something similar could be happening with *Cladophialophora bantiana*, although the number of published systemic infections with this fungus is very much greater than with *Exophiala dermatitidis*. Until the search for the natural behaviour of *Cladophialophora bantiana* is concluded successfully, it remains a hidden threat to human health.

2. Candida auris: the ultra-fast emerging problem

Candida auris is a human pathogenic yeast species, which causes bloodstream infections in hospitalized patients with severe immune disorders. Differing from *C. albicans*, the fungus is resistant to commonly used antifungals and spreads with an amazing speed, causing outbreaks on a global scale.

Why is Candida auris different from other Candida species?

Candida species are part of the normal commensal skin and gut microbiota of healthy individuals and they are ubiquitous in numerous natural and artificial habitats. When the balanced interaction between these yeasts and the human host is disrupted, for example as a result of surgery, some of these *Candida* species can transit from commensals to pathogens, overgrowing on skin and mucosal surface and/or invading the host tissue and disseminating into the bloodstream. The yeast can cause additional infection to other organs if the patient's immune system is weakened (Pappas et al. 2018).

Although *Candida albicans* is the most frequently isolated yeast species, many health care institutes reported a marked shift towards non-*albicans Candida*, most of which have alarming resistance to azoles such as fluconazole (Perlin et al. 2017). Typical non-*albicans Candida* species, such as *C. tropicalis*, *C. glabrata, C. krusei* and *C. parapsilosis,* are well-recognized nosocomial (hospital acquired) blood stream pathogens (Pappas et al. 2018). Only very recently, *C. auris,* a multidrug-resistant nosocomial pathogen has globally emerged (Fig. 2) (Chowdhary et al. 2017; Jeffery-Smith et al. 2018; Tsay et al. 2018; Kohlenberg et al. 2018; Lamoth and Kontoyiannis 2018; Saris et al. 2018). In less than a decade, this difficult-to-treat and easily transmitted yeast has become the culprit of clonal outbreaks in several hospitals (Chowdhary et al. 2013, 2014; Schelenz et al. 2016; Eyre et al. 2018; Chow et al. 2018; Ruiz-Gaitán et al. 2018). In an Indian hospital it appeared recently as the second most common cause of candidemia (Mathur et al. 2018). These fungal healthcare-associated infections are reminiscent of and comparable to the well-known outbreaks due to multi-resistant bacteria,

Fig. 2 Global map depicting the rapid emergence of multidrug-resistant clinical *Candida auris* strains in five continents. Over 30 countries have reported patients with *C. auris*

such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* and extended spectrum beta-lactamase and carbapenemase producing Gram-negative bacteria. Given the known behaviour of these bacterial pathogens, a further spread of *C. auris* in healthcare settings on a global scale is expected. To make things worse, *C. auris* is able to contaminate the healthcare environment similar to the notorious bacterial pathogen, *Clostridium difficile* (Chowdhary et al. 2016; Tsay et al. 2018).

Candida auris should be handled with utmost care and is of public health importance because (1) it spreads horizontally within and between hospitals; (2) it can cause fatal diseases in vulnerable patients with reported mortality in less developed countries of up to 60%; and (3) once spread and disseminated in the hospital environment it is difficult to eradicate.

Why has Candida auris only been recognized as a pathogen in the last decade?

Candida auris is a member of the *C. haemulonii* species complex, a group of haploid yeasts known for their antifungal resistance, and was only described as late as 2009 from a human external ear canal (Satoh et al. 2009). The very first reported three cases of nosocomial fungemia (presences of fungi in blood) due to *C. auris* in 2011 from South Korea alerted us to the fact that misidentification as *C. haemulonis, Rhodotorula glutinis* (Lee et al. 2011), *Candida famata*, *C. lusitaniae*, *C. guilliermondii*, or *C. parapsilosis* by commercial phenotypic identification systems was a potential threat in missing the correct identification (Mizusawa et al. 2017; Lockhart et al. 2017a, b; Snayd et al. 2018). The earliest reported isolate of *C. auris* known so far dated from 1996 and was detected in a Korean culture collection (Lee et al. 2011). Due to the close phylogenetic relationships to other members in the complex (*C. haemulonis*) it is reliably identified based on sequence analysis of the D1/D2 domain of the 26S rRNA gene and the internal transcribed spacer (ITS) regions of the nuclear rRNA gene operon. A study looking for *C. auris* presence among 102 clinical isolates, previously identified with phenotypic methods as *C. haemulonis* or *C. famata*, actually found that, by ITS sequencing, 88% of the isolates were in fact *C. auris* (Kathuria et al. 2015). Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) is considered the identification method of choice at present (Kathuria et al. 2015; Girard et al. 2016; Bao et al. 2018). Obviously it is of clinical significance to identify *C. auris* correctly in order to provide optimal patient care and to take timely and appropriate infection control precautions. We do not know the origin of this emerging fungal pathogen and for how long it has already been present in the human–environment.

Does the genetic background of Candida auris contribute to virulence?

The rapid emergence of *C. auris* might be linked to species-specific, previously unknown virulence determinants. Studies of the whole genome (WG) of *C. auris* show that it has a size of approximately 12.3 Mb with a significant percentage of genes involved in central metabolism, common to other pathogenic *Candida* species and which are important for adaptation to different environments. Furthermore, a significant portion of the *C. auris* genome encodes the ATP-binding cassette (ABC) and major facilitator superfamily (MFS) transporter families along with drug transporters that may explain the exceptional multidrug resistance and biofilm forming capacity (Muñoz et al. 2018). Comparison of WG sequencing data shows *C. auris* to be a close phylogenetic relative of *C. lusitaniae*, a species recognized for intrinsic antifungal resistance (Muñoz et al. 2018). *Candida auris* also demonstrates thermotolerance up to 42 °C, shows salt tolerance, and forms large, difficult-to-disperse cell aggregates, which may help some strains to persist in the hospital environment (Borman et al. 2016). In a *Galleria mellonella* model and in mouse models, *C. auris* isolates exhibits pathogenicity comparable to that of *C. albicans*, which is the most pathogenic member of the genus (Borman et al. 2016; Ben-Ami et al. 2017; Fakhim et al. 2018). Unpublished data show that *C. auris* appears to be more virulent than *C. albicans* in Toll-deficient flies (Lamoth and Kontoyiannis 2018). Another significant factor involved in *C. auris* virulence is its ability to differentially adhere to polymeric surfaces, form biofilms, and resist antifungal agents that are active against planktonic yeast cells (Kean et al. 2018).

What are the drivers of clonal transmission and nosocomial outbreaks of Candida auris?

A recent temporal whole genome in-depth analysis of the first outbreak in the UK showed that the most recent common ancestor was only found in March 2015, just before the first confirmed hospital infections a few weeks later, suggesting a recent introduction into the UK (Rhodes et al. 2018). There is increasing evidence that the uncontrolled transmission of *C. auris* in healthcare settings is driving the quick emergence and spread in less than a decade (Meis and Chowdhary 2018). Persistent colonization by *C. auris* of hospital environments, equipment and multiple patient body-sites, was responsible for protracted outbreaks (Schelenz et al. 2016; Eyre et al. 2018; Ruiz-Gaitán et al. 2018). In large outbreaks in UK and Spanish hospitals the yeast persisted around bed-space area, mattress, bedside table, bed rail, chair, and windowsill. Genotyping with amplified fragment length polymorphism

and WG sequencing demonstrated that *C. auris* isolates are clonal within hospitals and regions with several reported geographically related clusters from South Korea, India, South Africa, Pakistan, and hospitals in Latin America (Escandón et al. 2018). A large-scale application of WG sequence data suggests recent independent and nearly simultaneous emergence of different clonal populations on three continents, with highly related *C. auris* isolates in the same geographic areas (Lockhart et al. 2017a; Chow et al. 2018). Despite intensive research, no animal, plant, or water natural reservoir of *C. auris* has yet been identified. Finding this source will be crucial in understanding the rapid emergence during the last decade.

Is antifungal resistance in Candida auris a therapeutic challenge?

Patients with *C. auris* infections have risk factors similar to those of infections by other *Candida* species. The overall crude in-hospital mortality rate of *C. auris* candidemia ranges from 30 to 60%, and infections typically occur several weeks (10–50 days) after admission (Chowdhary et al. 2013; Schelenz et al. 2016; Khan et al. 2018). Several studies mention breakthrough fungemia during fluconazole therapy and this correlates with a commonly reported 90% resistance (minimum inhibitory concentrations; MIC $>$ 32 μg/ml), suggesting acquired resistance against this drug. Echinocandins remain the first-line therapy for *C. auris* infections, provided that specific susceptibility testing is undertaken at the earliest opportunity. Resistance is probably inducible under antifungal pressure, resulting in rapid mutational changes (Chowdhary et al. 2018).

What are the important things we have learned about Candida auris?

We are just beginning to learn about the behaviour of *C. auris* which, as of now, has spread to 33 countries. The earliest findings of *C. auris* are from 1996. The pertinent question remains whether this pathogen existed long before 1996, and we were just unable to identify it. The latter is unlikely because many centers have reviewed archived isolate collections that have not shown any isolates of *C. auris* before 1996 (Lockhart et al. 2017b). We also do not know why *C. auris* almost simultaneously emerged in so many places worldwide. It is clear now that there is a profound phylo-geographic structure with large genetic differences among geographic clades, high clonality within the geographic clades and a probable introduction into the USA and Europe in the last 3 years (Meis and Chowdhary 2018). A common characteristic of all isolates is the high level of antifungal resistance for multiple drugs, which is rare in other *Candida* species. *Candida auris* is the only species with reported resistance to all four classes of registered antifungal drugs. Environmental factors play a major role in outbreaks in healthcare settings due to prolonged skin colonization of patients and asymptomatic carriers in addition to environmental contamination. Effective implementation of strict infection-prevention control measures are required to curb transmission of *C. auris* which include isolation of patients and their contacts, wearing of protective clothing by healthcare workers, meticulous screening of patients on affected wards and those transferred from regions or hospitals with known *C. auris* prevalence, skin decontamination with chlorhexidine, environmental cleaning with chlorine-based reagents, and terminal decontamination with hydrogen peroxide vapour or ultraviolet light (Chowdhary et al. 2016; Saris et al. 2018). Increased efforts by the medical community are necessary in controlling this alarming fungus before it adapts to our healthcare facilities as we have seen with the bacterial pathogens (Meis and Chowdhary 2018).

3. Talaromyces marneffei—from HIV to everyone, the two-faced travel companion

The fungus that was previously called *Penicillium marneffei* has emerged as one of the most common opportunistic infections of AIDS patients especially in the South-East Asia region where it is endemic. Now renamed *Talaromyces marneffei,* it causes talaromycosis resulting in disseminated disease which eventually leads to death. The fungus is the third most common infection in HIV patients, after tuberculosis and cryptococcosis.

History and clinical importance

Penicillium marneffei was identified and isolated for the first time in 1956 from a liver of a captive rodent (bamboo rat, *Rhizomyces sinesis*) used for experimental infections at the Pasteur Institute in Dalat, central Vietnam (Capponi et al. 1956). Some of the rats maintained in captivity died after inoculation experiments or succumbed even before inoculation took place. Culture from organs led to the discovery of the fungal pathogen. The involvement of the fungus in the rat reticuloendothelial system was then described, and the new species was named *Penicillium marneffei*, named after the Director General of the Pasteur Institutes in Indochina, Hubert Marneffe (1901–1970). Three years later the first human case of penicilliosis was reported by Gabriel Segretain who accidently inoculated himself in his finger while transferring the fungus. Nine days after infection, a small nodule appeared at the inoculation site, developing with a lymphatic series of nodules at the biceps. Inflammation remained, despite treatment with nystatin. Thanks to his intact immunity, the infection remained localized. Di Salvo et al. (1973) described the first natural infection in an American who had Hodgkin's disease and who had been living in Southeast Asia. This patient underwent splenectomy and the cultivation of

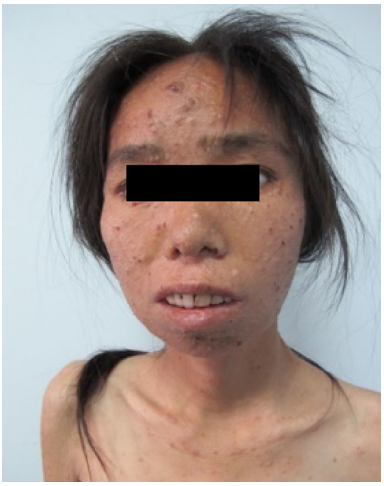

Fig. 3 AIDS patient from China with disseminated *Talaromyces marneffei* infection visible as cutaneous papules all over the body. Courtesy Xie Zhi, Department of Dermatology, Nanning, China

necrotic materials of spleen and growth at 37 °C exhibited *P. marneffei*, identified with certainty by the presence of yeast-like cells. Pautler et al. (1984) described a further case in a patient from Florida who suffered from hemoptysis (coughing up of blood from the lungs) and had travelled to Southeast Asia. During the same year, five cases were reported in Thailand (Jayanetra et al. 1984), and eight more by Duong (1996) in China. HIV-association of the species was first noted by Piehl et al. (1988) in an AIDS patient suffering from tuberculosis and with a history of travel to the endemic area of Southeast Asia. Soon the fungus became an AIDS-defining disease in endemic regions (Maniar et al. 2005). Soon disseminated penicilliosis with characteristic, papular skin lesions in patients with AIDS in South-East Asia (Fig. 3) became one of the most common opportunistic infections during the end stage of disease. Immunity against *P. marneffei* is largely mediated by macrophages, but the fungus survives and remains and reproduces within cells of the mononuclear phagocyte system.

The sexual states of *Penicillium* are classified in *Eupenicillium*, while relatives of *P. marneffei* have quite distinct sexual stages in *Talaromyces* (Houbraken and Samson 2011). *Penicillium* appeared to be polyphyletic and therefore species of the former section *Biverticillum* (the other way round) which also differed by the shape of its phialides, were transferred to *Talaromyces* (Samson et al. 2011). The name of *P. marneffei* changed to *Talaromyces marneffei*, and consequently the disease name should be changed to talaromycosis. Yilmaz et al. (2014) further elucidated the genus *Talaromyces* with 88 species placed in seven sections. Six of these species are clinically relevant (de Hoog et al. 2018).

Dimorphic transition

Talaromyces marneffei undergoes morphological transition in response to temperature, developing as filamentous hyphae during its saprotrohic stage at 25 °C, and as yeast-like cells at 37 °C and in host tissue. *Talaromyces marneffei* is the only dimorphic species in the genus. Between 25 and 30 °C, growth is rapid (Duong 1996), white-greyish, feathery and woolly. A red pigment diffuses around the colonies, as is observed in many *Talaromyces* species. With age, the colonies become rough and the mycelium turns yellow. After 2 days of incubation at 37 °C, no red pigment is produced. *Talaromyces marneffei* grows at temperatures up to 39.8 °C, with transition to the yeast-like form starting out at 32 °C (Cao et al. 2007). The conidiophores are mostly biverticillate, 70–150 × 2.5–3 µm (Vanittanakom et al. 2006).

The yeast-like phase at 37 °C is actually arthroconidial, cells being produced by fission of pre-existing filaments, on artificial media as well as in human macrophages (Vanittanakom et al. 2006). The conidia on the filamentous form would be responsible for infection after inhalation, while the yeast cells, found in macrophages and histiocytes (Andrianopoulos 2002), are the invasive form. In this respect, *T. marneffei* behaves similarly to onygenalean dimorphic fungi, such as *Histoplasma capsulatum* and *Blastomyces dermatitidis* (Boyce and Andrianopoulos 2015).

Reservoirs of Talaromyces marneffei

Many studies have been conducted to illustrate the life cycle of zoonotic *Talaromyces marneffei* since its discovery in the bamboo rat *Rhizomys sinensis* and later in the internal organs of related rat hosts (*R. pruinosus*, *R. sumatrensis* and *Cannomys badius*) (Chariyalertsak et al. 2002). Huang et al. (2015) found *T. marneffei* in Guangdong Province, China in 15 out of 270 environmental samples. Six captured rats were carriers of *T. marneffei* in lung, liver and spleen, but were in good health. Intestines and embryos were unaffected, and thus vertical transmission is excluded. Cao et al. (2011) demonstrated that some of the strains of *T. marneffei* infecting humans were the same as those in bamboo rats. Thus, bamboo rats are a main reservoir for *T. marneffei*, with a prevalence of about 70% (Li et al. 2011). Dogs might be an additional animal reservoir in northern Thailand (Chaiwun et al. 2011). Another suggested association with animals is with elephants (Pryce-Miller et al. 2008).

Transmission routes

Soil exposure may be imperative in acquiring primary infection of the organism. However, *T. marneffei* has never been isolated from the environment as its ecology outside the bamboo rat remains obscure. Bamboo rats and HIV-positive patients have been found to share genetically similar strains of *T. marneffei*, suggesting either rat-to-

human transmission or co-infection from a common source (Gugnani et al. 2004). In endemic areas, talaromycosis affects both rural and urban inhabitants. According to Chariyalertsak et al. (1997), contact with bamboo rats is not a risk factor for talaromycosis, but is due to agricultural work during the rainy season. Le et al. (2010) showed a peak in *T. marneffei* infections in Vietnam around August, during the rainy season. Bulterys et al. (2013) provided similar data from a large-scale study conducted between 2004 and 2010. Thus, high humidity rather than dry dust seems to play a role in *T. marneffei* infection. There is no evidence of human-to-human transmission: patients are not contagious. Ingestion has also been suggested, as people in southern China eat bamboo rats which might be infected with *T. marneffei*. In addition, direct inoculation of skin could be another mode of transmission.

Current epidemiology in humans

The infection is recognized as potentially fatal in an advanced stage of HIV infection (Hu et al. 2013). Disseminated talaromycosis is limited to Southeast Asia, southeast China, Taiwan and Hong Kong. It is now the third most common infection in HIV patients, after tuberculosis and cryptococcosis (Wong and Wong 2011). Talaromycosis affects AIDS patients of all ages (Son et al. 2014), while 87–96% are males (Vu Hai et al. 2010). Notably, the risk of infection is not restricted to those living in endemic areas, but frequently occurs when visiting those areas, becoming fulminant when the patient has returned home. Clinicians should be aware of this delayed appearance of the disease, and ask for the patient's travel history (Julander and Petrini 1997).

Talaromycosis has become an important risk to travellers with impaired acquired immunity, particularly when visiting Vietnam, Laos, Malaysia, Myanmar, East India, Thailand and the Guangxi Province in southeastern China. Organ transplant recipients from donors originating from these regions are also at risk (Hermans et al. 2017). For India, Gugnani et al. (2004) confirmed that the reddish-brown bamboo rat (*Cannomys badius*) is a source of talaromycosis. Travel-associated cases occur globally. A 36-year-old US patient with HIV suffered from talaromycosis 4 months after a 6-week trip to India and Southeast Asia (Carey et al. 2005). Cases were also described in HIV patients in the non-endemic countries Argentina and Togo (Santiso et al. 2011; Patassi et al. 2013). An HIV positive individual travelled to Thailand and returned to England with talaromycosis (Hall et al. 2013). Mohsin et al. (2017) diagnosed *T. marneffei* in an HIV positive patient in Oman who had travelled to Malaysia on several occasions.

Today, the infection also occurs outside the HIV community. A 71-year-old HIV-negative Japanese patient, who returned to his country after living in Thailand for several years, was diagnosed with talaromycosis (Furusawa et al. 2014). In a similar case, a 39-year-old HIV-negative patient in South Korea had lived in Laos for several years (Jung et al. 2012). An Australian kidney transplant recipient was infected after 10 days of vacation in Vietnam (Hart et al. 2012). Another organ transplant recipient who has developed disseminated disease after travelling to an endemic area was reported by Chan et al. (2015). A French patient with chronic obstructive pulmonary disease (COPD) regularly inhaled corticosteroids and was diagnosed with talaromycosis a decade after a trip to China (De Monte et al. 2014).

Why should Talaromyces marneffei be feared?

The mortality rate of untreated *T. marneffei* infections in HIV-infected patients is 100% (Supparatpinyo et al. 1993). Given the widespread increase in the prevalence of talaromycosis in Southeast Asia, the potential of human infection needs to be reassessed. The incidence of *T. marneffei* infection has decreased since the introduction of highly active antiretroviral therapy (HAART) in HIV patients, but the worrying increase of *T. marneffei* infections among HIV-negative individuals with other types of impairment of cell-mediated immunity, such as those who have undergone organ transplantation (Hermans et al. 2017) or otherwise debilitated patients (Furusawa et al. 2014) expands the susceptible population significantly. Non-HIV-infected individuals are frequently misdiagnosed as having other diseases (Chan et al. 2016). In addition, in vitro susceptibility testing shows that the fungus is highly resistant to fluconazole (Sar et al. 2006). The survival rate of patients treated with an appropriate antifungal agent was significantly higher than the individuals without treatment, which means that timely and accurate diagnosis is key to an increased survival rate.

Another challenge is that the management of infected patients is often impeded due to an unknown duration of the incubation period (Kawila et al. 2013). Reactivation of latent infections may occur in patients with CD4 cell counts < 100 cells/mm^3 (Chaiwun et al. 2011), many years after residence in an endemic area. Some holiday travellers returning from endemic areas developed symptoms a few weeks after their return, while others contracted the disease years later. For example, De Monte et al. (2014) described the case of a French patient with chronical obstructive pulmonary disease, who travelled to Thailand in 1979 and to China in 2002, and was diagnosed with talaromycosis late in 2012. This suggests that *T. marneffei* may remain latent as an intracellular pathogen, and is reactivated during a period of weakened immune defense (Wong and Wong. 2011).

4. Malassezia globosa: the dandruff fungus

Most humans consider themselves to be a single organism or entity. However, it is now accepted that we are more a

very complex ecosystem—a group of millions of individual cells, as many microbial organisms as human cells. When this ecosystem exists in harmony, all is well. However, when the system is perturbed (for microbes termed "dysbiosis") illness is often the result. Every human and every warm-blooded mammal so far studied was found to be covered by a microbial community where the fungi (i.e., the human mycobiota of the skin) are dominated by a specialized yeast, *Malassezia*. As you read this article, it is very likely that skin flakes containing *Malassezia* are dropping on this page (or keyboard).

Malassezia spp. are basidiomyceteous yeasts primarily occurring as normal (commensal) occupants of human and animal skin. However, they are also involved in many of the most common skin disorders, including dandruff, seborrheic dermatitis, psoriasis, atopic eczema, pityriasis versicolor, and possibly acne (Prohic et al. 2016), thus playing a negative role in almost every human at least at some point in their lifetime. *Malassezia* represent by far the most abundant fungal component of the healthy human skin (Byrd et al. 2018), which simultaneously enables them the necessary exposure to take on a pathogenic (occasionally lethal) role. Some are able to invade the bloodstream of the most vulnerable of humans and cause bloodstream infections in immunocompromised individuals, most notably young children, and neonates (Iatta et al. 2014; Ilahi et al. 2018; Theelen et al. 2018). Furthermore, *Malassezia* spp. have been suggested to play a role in skin carcinogenesis as they produce an array of aryl-hydrocarbon receptor (AhR) ligands, allowing them to mediate ultraviolet damage and to modulate the host immune response. Additionally, colocalization of *Malassezia* yeasts with basal cell carcinoma has been observed (Gaitanis et al. 2011, 2012). Furthermore, *Malassezia* even colonize and cause disease in many animals, causing common and difficult to treat disorders such as ear infections (*otitis externa*) and severe dermatitis. Due primarily to a lack of research tools, but also because of limited funding, little data are available about their incidence and pathogenic impact in animal skin (Bond et al. 2010).

Phylogenetically, the genus *Malassezia* constitutes a deeply rooted, basal evolutionary lineage within the Ustilaginomycotina (Wang et al. 2014). Their placement among primarily plant pathogenic fungi has led researchers to ponder why fungi so closely related to plant pathogens are found on the skin of all humans. *Malassezia* are uniquely lipid-dependent, one of multiple traits which probably evolved to assist in their utilization of humans as a food source (Wu et al. 2015). From their discovery in 1889 to the late 1990s, the genus comprised only two species, *Malassezia furfur* (Fig. 4) and *Malassezia pachydermatis*, but taxonomic breakthroughs led to the description of multiple new species from human and animal hosts and the genus currently consists of 18 species. The most recently described species, *Malassezia vespertilionis*, was isolated from a bat and is able to grow at much lower temperatures than other *Malassezia* species, supporting multiple recent non-culture based studies that describe *Malassezia* in much wider ecological niches, including terrestrial and marine ecosystems, temperate and Antarctic soils, corals, sponges, nematodes, and cone snails (Amend 2014; Lorch et al. 2018; Theelen et al. 2018).

Human skin disorders

In humans, *Malassezia* are the cause of the common skin disorders dandruff/seborrheic dermatitis, *Malassezia* folliculitis, and pityriasis versicolor, and are associated with atopic dermatitis and psoriasis. Although not life-threatening, they have a detrimental impact on physical and psychological comfort and quality of life, especially since the effects are so visible.

Dandruff and seborrheic dermatitis affect the sebaceous skin, with dandruff restricted to the scalp and seborrheic dermatitis (a human skin disease affecting scalp, eyebrows,

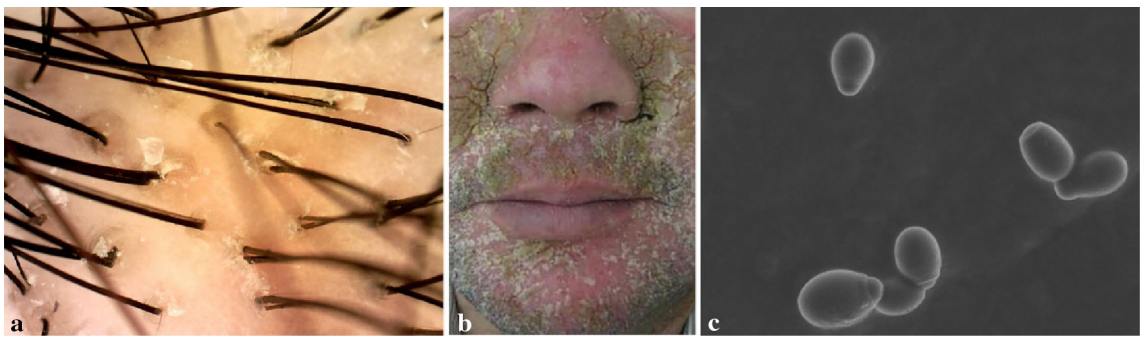

Fig. 4 *Malassezia.* **a** Scalp with severe flaking from patient suffering from dandruff. **b** a case of postherpetitic seborrheic dermatitis (SD) - courtesy of Yuping Ran, Department of Dermatovenereology, West China Hospital, Sichuan University, Chengdu, P.R. China. and **c** Scanning Electron Microscopy (SEM) picture of *Malassezia furfur*—courtesy of Jan Dijksterhuis, Westerdijk Fungal Biodiversity institute, Utrecht, the Netherlands

facial hair, and the nasolabial fold). Both result in itchy, flaking skin, and seborrheic dermatitis is more severe with visible inflammation. Dandruff is very common, affecting approximately 50% of the adult population. It is estimated that in the USA alone, 50 million people suffer from dandruff, with nearly $10 Billion USD per year spent globally on treatment (Borda and Wikramanayake 2015). Pityriasis versicolor is a superficial infection of the stratum corneum causing hypo- or hyperpigmentation on the trunk and upper arms accompanied with fine scales and itching and increased sweating. It is most prevalent in summer and affects up to 50% of people in tropical areas. The disorder is most common among adolescents and young adults (Renati et al. 2015). In atopic dermatitis, *Malassezia* interacts with the host immune system, leading to chronic skin inflammation with acute eczematous itching lesions (Grice and Dawson 2017; Nutten 2015). It affects 15–20% of children and 1–3% of adults worldwide and its incidence has increased 2- to 3-fold in industrialized countries during the past decades. Atopic dermatitis may be an initial stage in a progression called the "atopic march" where the patients develop asthma and allergic rhinitis (Nutten 2015).

Bloodstream infections

Multiple studies reveal an increasing incidence of systemic fungal infections in immunocompromised patients (Gaitanis et al. 2012; Iatta et al. 2014). Identification of *Malassezia* in clinical practice requires special growth media and long culture times, making it likely that these reports vastly underestimate the number of actual Malassezia-related infections. While the most common fungal pathogen of humans are *Candida* spp., *Malassezia furfur* and *M. pachydermatis*, and a few cases of *M. sympodialis* have also been identified as the causative species (Iatta et al. 2014; Theelen et al. 2018). A specific patient group at risk for *Malassezia* infection is neonates receiving nutrition intravenously with lipid supplementation. Clear data on the global incidence remain elusive due to the aforementioned difficulty in identification, but a recent one-year survey of bloodstream infections with *Malassezia* and *Candida* in a neonatal intensive care unit and in a surgical pediatric ward in the south of Italy showed a prevalence of 2.1% *M. furfur* over 1.4% *Candida*-related infections in 307 patients monitored (Iatta et al. 2014). In a survey of neonates from Moscow between May 2012 and December 2015, 21,192 samples (blood, urine, catheter) from 3302 neonates were analyzed and 4% of the samples were found positive for fungi, of which 67% was *M. furfur* (Rodchenko et al. 2016). *Malassezia* bloodstream infections can be managed by catheter removal, temporary discontinuation of lipid parenteral nutrition in combination with intravenous antifungal therapy with liposomal amphotericin B, and there are cases where pathogenic *Malassezia* are multi-azole resistant (Kim et al. 2011; Iatta et al. 2016).

Many aspects of *Malassezia* pathophysiology remain elusive. Their presence on both healthy and diseased skin poses a challenge for elucidating the transition between commensal and pathogen states. The full impact of *Malassezia* infections of humans and animals is underdiagnosed, due to the lack of lipid supplementation in culture media that are routinely used in hospitals. Traditionally used identification methods based on morphological and biochemical features do not always result in accurate species identification, which is important for correct diagnosis and treatment.

In recent years, new tools for cultivation, genomic speciation, and genetic engineering have enabled the genus *Malassezia* to gain increased attention from the scientific and clinical communities. Much new knowledge has been obtained about its ecology, presence in the skin microbiome, pathology, clinical relevance, and incidence. High quality and well annotated genome sequences are available for *M. restricta*, *M. globosa* and *M. sympodialis* and Illumina genome sequences for most other species, offering a wealth of information for further analysis (Wu et al. 2015; Theelen et al. 2018). The successful development of transformation and genetic engineering in *Malassezia* will contribute to the functional analysis of suspected pathogenicity related genes and will help to further clarify the complex role of *Malassezia* in health and disease (Ianiri et al. 2016; Celis et al. 2017).

Other human pathogens

Apart from these top four feared fungi, *Cryptococcus* and *Pneumocystis* require attention due to their medical importance. The *Cryptococcus neoformans*/*C. gattii* (Basidiomycota) species complex (Fig. 5) are among the most common fungal pathogens in humans and animals worldwide and they cause cryptococcosis, which remains one of the leading causes of acquired immunodeficiency syndrome (AIDS) related deaths in humans (Kwon-Chung et al. 2014). These two species complexes are classified into five serotypes (*C. neoformans* serotype A, D and AD, as well as *C. gattii* serotype B and C) and their taxonomy has been thoroughly revised (Hagen et al. 2015). The two varieties of *C. neoformans* were recognised as species, with *C. neoformans* (formerly *C. neoformans* variety *grubii*) and *C. deneoformans* (formerly *C. neoformans* variety *neoformans*) (Hagen et al. 2015), while the *C. gattii* genotypes were raised to the species level as *C. gattii* sensu stricto (VGI), *C. bacillisporus* (VGIII), *C. deuterogattii* (VGII), *C. tetragattii* (VGIV/AFLP7) and *C. decagattii* (VGIV/AFLP10) (Hagen et al. 2015).

Cryptococcal infections often lead to pulmonary and central nervous system diseases, the latter being a major

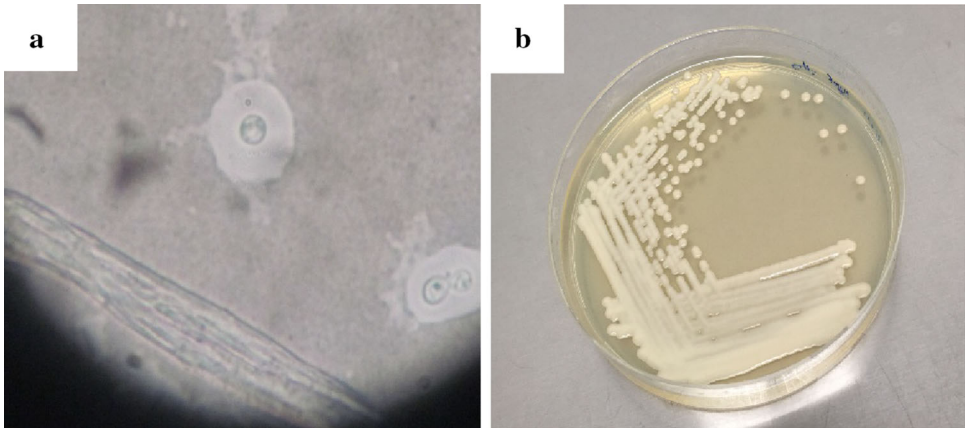

Fig. 5 **a** *Cryptococcus* isolates showing the capsule under microscope examination (× 400). **b** Culture on 10% Sabouraud Dextrose agar at 30 °C for 48 h

source of mortality and morbidity (Kwon-Chung et al. 2014; Skolnik et al. 2017). *Cryptococcus neoformans* and *C. deneoformans* infections are common in immunocompromised patients and HIV-infected adults; more than 1 million AIDS patients are infected with *C. neoformans* annually and most of these patients will die in a few months of diagnosis (Park et al. 2009). *Cryptococcus neoformans* also infects those receiving organ transplants or immune-suppressive medications (including chemotherapy and cytotoxic therapies (Skolnik et al. 2017)). By contrast, *C. gattii* species complex causes infections mainly in immunocompetent patients and is geographically restricted to tropical and subtropical climates, leading to its characterization as an endemic mycosis (Kwon-Chung et al. 2014; Skolnik et al. 2017). However, members of the *C. gattii* species complex have increasingly been reported in temperate regions. For example, since 1999 specific genotypes of *C. deuterogattii* (VGII) have caused outbreaks of cryptococcosis on Vancouver Island, Canada and Pacific Northwest in the USA, indicating a strong shift in its ecological niche (Kidd et al. 2004; Byrnes et al. 2009). In addition, infections caused by *C. gattii* tend to be more severe than the ones caused by *C. neoformans* resulting in pulmonary mass lesions after prolonged asymptomatic infections, which then need longer treatments (Kwon-Chung et al. 2014). It is clear that both species complexes are important clinically and present challenges in diagnosis and treatment.

Pneumocystis jirovecii is another unicellular fungal pathogen responsible for HIV-associated morbidity and mortality (Huang 2011), and for at least one quarter of all pneumonia deaths in HIV-infected infants (http://www.who.int/news-room/fact-sheets/detail/pneumonia). Transmission of *P. jirovecii* happens through the aerial route. Since *P. jirovecii* is an obligate extracellular pathogen and exists in trophic and cystic forms and is hard to obtain in culture, its biology/virulence mechanism is not well-understood (Morris and Norris 2012). Initially, *Pneumocystis* spp. had been even considered to be protist, rather than fungi. *Pneumocystis jirovecii* remains a significant cause of mortality among HIV-negative patients undergoing immunosuppression caused by different factors, such as transplant, and is re-emerging as a growing public health concern. *Pneumocystis* has been detected in the bronchoalveolar lavage (BAL) fluid of 33% of HIV-infected patients presenting with a diffuse pneumonia in southern Africa (Malin et al. 1995).

We have deliberately left out *Aspergillus fumigatus* and other fungi that are often reported as opportunistic pathogens, but wish to point out the great danger that arises from the numerous reports of azole-resistant clinical isolates that are steadily being encountered (Verweij et al. 2015). In a similar manner as in case of the antibacterial antibiotics, the development of new antimycotics has lamentably been neglected and the drugs used for treatment of human diseases caused by fungi heavily relies on the same classes of molecules that are being used as agrochemical fungicides. Environmental strains of *A. fumigatus* and other fungi that have become resistant against azoles may enter the hospital and cause very serious disease symptoms there in immunocompromised patients, whose number will inadvertently increase further in the future due to demographic developments. Hence, the number of fatalities caused by opportunistic human pathogenic fungi may substantially increase in the future, unless measures will be undertaken to substantially improve their diagnostics and therapy.

Human health

Fungi not only cause human disease but can also have other serious consequences for our health. The two most important concerns are the fungi that grow on our food and produce mycotoxins and the indoor air fungi that may cause serious medical complications when their spores are inhaled. Thus, we choose *Aspergillus flavus*, an aflatoxin producing species that grows on our food, to represent the

5th most feared fungus and *Stachybotrys chartarum*, which grows in our houses and causes health problems to represent the 6th most feared fungus. Although only some of the population collect and consume wild mushrooms, the death of humans due to consumption is often reported in the-media: therefore *Amanita phalloides* which is probably the most deadly of all wild mushrooms is chosen as the 7th most feared fungus.

5. Aspergillus flavus—the aflatoxin producing fungus

Few fungi have such a crucial public health and economic impact as *Aspergillus flavus*. This significance is, reflected by the high number of *A. flavus* related articles (almost 5000) that can be retrieved in bibliographic databases such as Web of Sciences or PubMed. It is explained by three main rationales: (1) *A. flavus* is the second most important *Aspergillus* species causing animal and human infections; (2) *Aspergillus flavus* can infect staple and dietary supplemental crops, resulting in yield and crop value losses; (3) after colonization of crops, *A. flavus* can overproduce the aflatoxin B1 which is among the most toxic and potent hepatocarcinogenic natural compounds ever characterized. The aim of the present review is to pinpoint the key topics regarding *A. flavus* and provide some relevant associated scientific publications. For more detailed and comprehensive information, we strongly encourage the readers to consult the high-quality reviews that have been published on *A. flavus* (Scheidegger and Payne 2003; Klich 2007; Amaike and Keller 2011) and/or on the aflatoxin type mycotoxins (Kensler et al. 2011; Kumar et al. 2016).

Taxonomy of Aspergillus flavus

In the current taxonomic system, *A. flavus*, which was first described by Link (1809), belongs to the phylum Ascomycota, the order Eurotiales, the class Eurotiomycetes and the family Trichocomaceae (Wijayawardene et al. 2018). Several whole-genome sequencing projects for *A. flavus* have been reported (e.g., for the most recent ones, Faustinelli et al. (2016) and Weaver et al. (2017)). All the provided data agree on a 36.8 Mb estimated genome size and approximatively 12,000 predicted functional genes. It should be noted that, the name of *A. flavus* is used to describe a species as well as a complex of closely related species (Hedayati et al. 2007). The wide variation occurring inside the *A. flavus* complex was corroborated once again by the recent study of Okoth et al. (2018) and recently reviewed by Frisvad et al. (2019).

Ecology

Aspergillus flavus is a saprotrophic fungal pathogen that spends a large part of its life growing in the soil and overwinters either as mycelia or as sclerotia (Wicklow et al. 1993). It is also a facultative and opportunistic fungal pathogen of both animals and plants with a worldwide distribution facilitated by the production of numerous airborne conidia that can easily disperse by air currents, and potentially by insects. Climatic and geographical conditions significantly influence the local prevalence of *A. flavus*; the fungus is isolated from a wide range of climatic zones, but has a higher frequency between latitudes in warm climate zones (Klich 2007). In fields, *A. flavus* preferentially infects oil-rich crops, such as maize, peanut, cottonseed and tree-nuts. Infection of crops is generally associated with the contamination of harvests with the aflatoxin B1 mycotoxin. Postharvest infection of seeds is also an alarming problem in several areas of Africa and Asia. Improper storage conditions such as excessive heat, high humidity, lack of aeration, and insect and rodent damage, which are common in the tropics, are conducive to *A. flavus* and its production of aflatoxin B1 (Villers 2014).

Why fear Aspergillus flavus?

There is serious concern regarding the potential animal and human health outcomes related to *A. flavus*, that could result from exposure to spores and/or to the aflatoxin B1 mycotoxin. Aerosolized *Aspergillus* spores are found nearly everywhere. Spores of *A. flavus* are particularly prevalent in outdoor air of some tropical countries. Nevertheless, *A. flavus* has also been reported as a frequent airborne fungal pathogen in north temperate countries (Hedayati et al. 2007). Additionally, *A. flavus* is common in indoor environments, frequently recovered in home and hospital air (Mousavi et al. 2016). In fact, exposure to *A. flavus* spores is a normal part of the human condition, but most humans have efficient immune systems that eliminate the spores. However, when immune systems are weakened, inhaling *A. flavus* spores may cause multiple diseases referred to as aspergillosis. *Aspergillus flavus* is acknowledged as the second cause of invasive and non-invasive aspergillosis, after *Aspergillus fumigatus*. Aspergillosis includes allergy, airway or lung invasion and cutaneous infection, but also aspergilloma that is related to a granulomatous disease of the lung and invasive aspergillosis, in which the fungus disseminates throughout the body (Misch and Safdar 2016). As of now, invasive aspergillosis caused by *A. flavus* remains one of the leading causes of morbidity and mortality in immunocompromised patients (including organ transplant patients) around the world (Amaike and Keller 2011). The number of invasive aspergillosis cases is anticipated to increase with the increased number of immune suppressed individuals within the human population and with the sometimes insufficient effectiveness of marketed antifungal drugs against severe fungal infections. Aspergillosis is therefore predicted to become a significant challenge for health care systems worldwide.

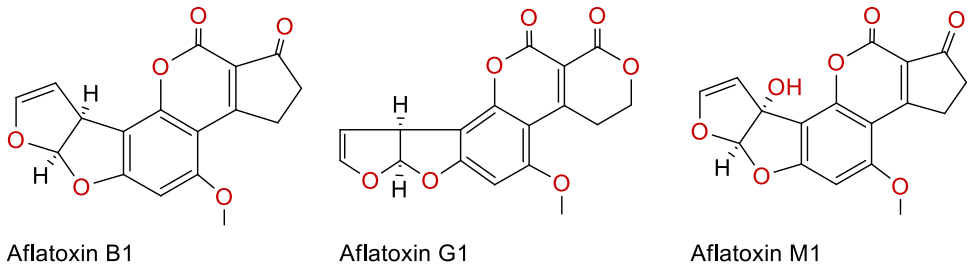

Fig. 6 Chemical structures of the most important aflatoxins

In addition to aspergillosis, *A. flavus* is responsible for significant animal and human diseases through the consumption of feed and food contaminated with the aflatoxin B1 mycotoxin. The discovery of aflatoxins dates back to the early 1960s after outbreaks of disease and death in turkey poults fed with mold-contaminated peanut meals. Aflatoxins (Fig. 6) are a group of closely related difuranocoumarin derivatives, with aflatoxin B1 being the most prevalent and potent form of these toxins. Known and supposed health impacts of dietary exposure to aflatoxin, referred to as aflatoxicosis, have been clearly and in depth detailed in several reviews, among which are those published by Williams et al. (2004), Kensler et al. (2011) and Wu et al. (2014). The likelihood of aflatoxicosis in humans is increased by a limited availability of food and the consumption of moldy products, environmental conditions and particularly improper storage conditions of seeds, and lack of regulatory systems for aflatoxin monitoring and control (Williams et al. 2004). More than 500 million people, mainly in sub-Saharan Africa and in parts of Latin America and Asia, are exposed to aflatoxin B1 at enhanced concentrations that could potentially increase mortality and morbidity (Walte et al. 2016). A significant segment of these populations is also exposed to the aflatoxin M1 through the consumption of milk and dairy products. Aflatoxin M1 is a hydroxylated metabolite of aflatoxin B1 with carcinogenic, teratogenic and mutagenic properties, found in the milk of lactating animals that have consumed aflatoxin B1-contaminated feed. Because of climate change, aflatoxin B1 is also predicted to become a food safety issue of high concern in maize in Europe (Battilani et al. 2016).

Mechanisms of aflatoxin toxicity

The main mechanism underlying aflatoxin B1 toxicity is linked to the metabolisation of the toxin in the liver into an epoxide form (the aflatoxin-8,9-epoxide) that can bind to proteins or DNA (Kensler et al. 2011). According to the dose and duration of exposure to aflatoxin, acute and chronic forms of aflatoxicosis are distinguished. Acute severe intoxications associated with high doses of aflatoxin result in liver damage and subsequent illness or death. Typical symptoms include hemorrhagic necrosis of the liver, liver cirrhosis, bile duct proliferation, edema and lethargy (Williams et al. 2004). Major human outbreaks due to aflatoxin have been documented in Africa, India and Malaysia over the years. Most were associated with consumption of aflatoxin-contaminated homegrown maize such as in India in the 1970s and in Kenya in the early 1980s and more recently in 2004 and 2005 (Wu et al. 2014). Resulting in 317 cases and 125 deaths, the 2004 Kenyan aflatoxicosis outbreak that occurred in some rural areas in eastern and central provinces is one of the largest and most severe outbreaks of acute aflatoxicosis ever recorded. In Malaysia, epidemiologic investigations evidenced that the outbreak was not the result from maize consumption, but from aflatoxin-contaminated noodles.

The main health hazard associated with chronic form of aflatoxicosis is hepatocellular carcinoma, one of the most common cancer in the world. Since 1993, aflatoxin B1 has been classified as a known human carcinogen by the International Agency for Research on Cancer. Identification of aflatoxin B1 as an etiological agent of hepatocellular carcinoma results from numerous experimental and epidemiological studies and strong evidence was provided by the measure of biomarkers of exposure such as aflatoxin B1-albumin adduct. Actually, aflatoxin B1 is believed to be responsible for 4.6–28.2% of all global hepatocellular carcinoma cases (Liu and Wu 2010). Importantly, epidemiological evidence indicates that risk of hepatocellular carcinoma is also significantly increased by a concomitant exposure to aflatoxin B_1 and chronic infection with hepatitis B virus that is a common infection in developing countries, the two factors acting in synergy (Wu and Santella 2012). In addition, several animal and epidemiological studies have provided an increasing body of evidence supporting an important role of aflatoxin B1 in growth impairment in children. Aflatoxin B1 is also strongly suspected to impair human immunity. This ability to affect the immune function is however primarily documented by experiments conducted in animals or in animal cell cultures and data is still insufficient to ascertain its effect on the human immune system (Kensler et al. 2011).

Economic impact of Aspergillus flavus

Although difficult to precisely estimate, a significant economic impact arises from *A. flavus* infections, resulting from costs linked to human health impact (aspergillosis and aflatoxicosis), and crop yield losses due to fungal diseases, reduced crop value resulting from aflatoxin B1 contamination, losses in animal productivity and trade impacts. The economic consideration must also include the costs of aflatoxin B1 management linked to prevention, sampling, analysis, mitigation, litigation, and research. As regards aspergillosis, the report of Tong et al. (2009) clearly illustrates the strong economic impact of invasive infection on US hospital expenditures. More documented are the economic losses related to aflatoxin B1. For the United States corn industry, these losses may exceed several tens of millions and up to $1 billion for harvest years characterized by climate conditions conducive to aflatoxin contamination (Mitchell et al. 2016). When all crops potentially contaminated with mycotoxins (aflatoxin but even including other mycotoxins of *Fusarium* species such as fumonisin and deoxynivalenol) are considered, the annual losses due to mycotoxin contamination were estimated between $418 million to $1.66 billion for the US (Vardon et al. 2003). The cost of monitoring aflatoxin can reach up to as much as $50 million annually (Wu 2015). In developing countries, it is unfortunate that the main economic investigations have focused on market costs, while health-related costs have rarely been quantified, certainly as a result of the complexity of their assessment. Thus, the report by Robens and Cardwell (2003) indicated that contamination of crops in African countries leads to annual losses of more than $750 million. The additional costs arising from the European Union regulation on aflatoxin was estimated to be close to $670 million for food African exporters (Otsuki et al. 2001).

While eliminating *A. flavus* from any environment is not realistic, several efficient strategic interventions can mitigate contamination of food/feed with aflatoxin to acceptable levels (Luo et al. 2018). Since the contamination with aflatoxin can occur anywhere in the chain, control strategy requires a multifaceted approach combining pre and postharvest interventions. The increased knowledge on the environmental factors that promote *A. flavus* infection and the production of aflatoxin in seeds has allowed establishing Good Agricultural Practices that gather selection of tolerant genotypes, early timing for planting, adequate irrigation to avoid drought stress, control of insects and biocontrol strategies including the use of atoxigenic aspergillus strains (Amaike and Keller 2011). The postharvest strategy package recommended to reduce aflatoxins, combines interventions such as harvesting at maturity, rapid drying, insect and rodent control, mechanical or hand sorting of damaged seeds (Villers 2014). Use of binders to reduce availability of aflatoxin in the gastrointestinal tract could reduce adverse effects for livestock and poultry (Williams et al. 2004). All these methods associated with the establishment of regulatory limits and the implementation of monitoring actions have allowed eliminating most of harmful exposures in developed countries. In developing countries where aflatoxin

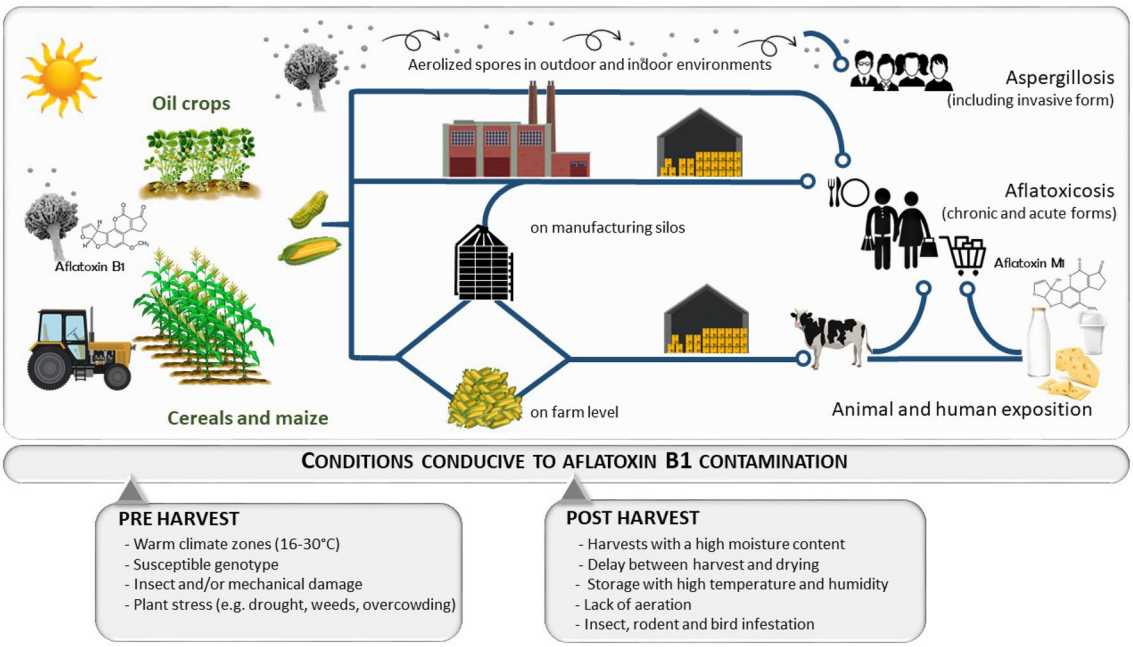

Fig. 7 Conditions conductive to aflatoxin B1 contamination

exposure is intertwined with the issues of food insecurity and insufficiency and where the technology and infrastructure such as the food production practices (with a prominence of subsistence farming) are not always appropriate to apply the previous methods, ensuring a low exposure to aflatoxin remains a significant challenge (Strosnider et al. 2006). In developing countries, in addition to investments in infrastructure, in pre- and postharvest technologies and implementation of a robust monitoring plan allowing an early warning system, a great emphasis should be placed on strategies promoting an increased public knowledge and awareness that will also result from an improved assessment of the costs arising from aflatoxin contamination (Udomkun et al. 2017) (Fig. 7).

6. *Stachybotrys chartarum*: the uninvited lodger

Stachybotrys is not often seen in nature, but becomes visible when it grows on wet cellulose-rich plant debris. It is an ascomycete belonging to the Hypocreales and produces its characteristic black spores in slime heads and, if conditions are right, can turn the media black within a few days (Fig. 8). In manmade environments two species are common: *Stachybotrys chartarum* and its sister species, *S. chlorohalonata,* which have a preference for severely water damaged textile, paper, cardboard and gypsum wallboard (Fig. 9). *Stachybotrys* is often seen in the aftermath of flooding in Europe and North America; however, in the tropics *Stachybotrys* seems to be replaced by the related genus *Memnoniella* (Miller et al. 2003). Recent research has shown that *Stachybotrys* spores can be found embedded in new gypsum wallboard (Andersen et al. 2017), meaning that water is the only prerequisite for a building to become black with mould growth.

Why fear Stachybotrys

Aided by the media, the fear of toxic black mould, i.e. *Stachybotrys,* was sparked by an outbreak of pulmonary haemorrhage (PH) in infants in Cleveland, Ohio, in 1993 (Etzel et al. 1998). Several additional cases have emerged since that also implicated *Stachybotrys* in infant pulmonary haemorrhage, but conclusive evidence is missing (Nelson 2001; Ammann et al. 2008). Public concern has sparked numerous help sites on the net and a Google search on "toxic black mold" returns 13,200,000 hits (20-08-2018).

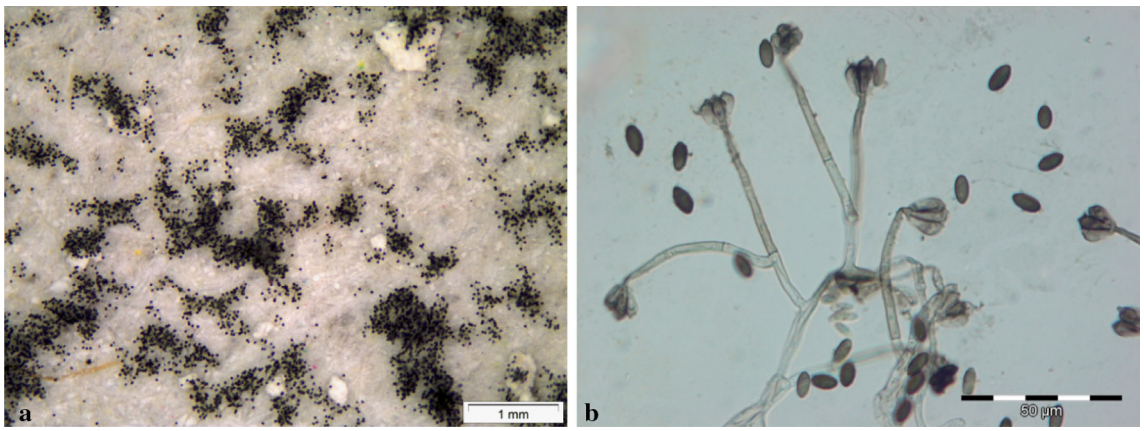

Fig. 8 *Stachybotrys* **a** slime heads on gypsum wallboard (scale bar 1 mm). **b** Conidia and conidiophores (scale bar 50 µm)

Fig. 9 *Stachybotrys* **a** growing on water saturated pipe insulation due to a leaking pipe (water drops can be seen hanging from the insulation), **b** on gypsum ceiling tiles after severe condensation in a basement

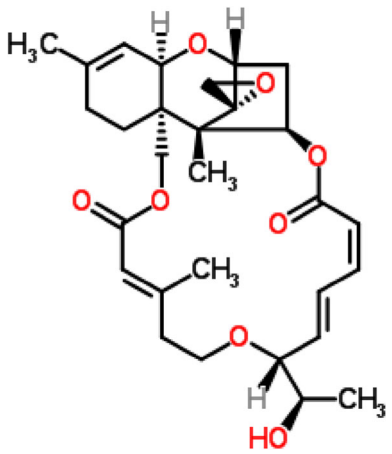

Fig. 10 The chemical structure of roridin E

In agriculture, *Stachybotrys* has been known for at least 100 years, where it causes illness in farmworkers and death in livestock (Nelson 2001; Miller and McMullin 2014). In the late 1930s, Russian workers, sleeping on straw-filled mattresses, experienced dermatitis, inflammation and bloody rhinitis (Nelson 2001). Hungarian workers handling mouldy straw complained of nose-bleeds (Harrach et al. 1984) and in Germany workers in a greenhouse developed inflamed lesions on their fingers after handling *Stachybotrys* infested plant pots (Dill et al. 1997). In South Africa, more than 100 sheep died after eating *Stachybotrys* infected feed (Schneider 1979) and 800 donkeys, mules and horses perished in Morocco in 1991 from stachybotryotoxicosis (Le Bars and Le Bars 1996).

In our indoor environments, *Stachybotrys* became a major concern 25 years ago because of the Cleveland cases and because occupants and building workers began to show adverse health effects similar to the farmworkers. In one case three workers clearing out a basement full of *Stachybotrys* infected cardboard boxes suffered acute responses, such as throat irritation, fatigue, fever, muscle and stomach aches and rashes on their hands. Later trichothecenes, a group of very biologically active *Stachybotrys* mycotoxins, were detected in the cardboard (Miller and McMullin 2014).

Health effects

Stachybotrys chartarum produces two chemotypes. Chemotype S produces macrocyclic trichothecenes (e.g., roridins (Fig. 10)), while chemotype A and *S. chlorohalonata* both produce atranones and simple trichothecenes (Andersen et al. 2003). Both indoor species produce spirocyclic drimanes (Miller and McMullin 2014) and new *Stachybotrys* metabolites are still being discovered (Jagels et al. 2018). During growth *Stachybotrys* also produce a sticky exudate on top of the mycelium. Gareis and Gottschalk (2014) showed that *S. chartarum* was able to produce 230–740 ng roridin E per ml exudate. A later study showed that roridin E and spirocyclic drimanes could be detected in dust in rooms adjacent to a water damaged bathroom (Došen et al. 2016) and recently it has also been demonstrated that *Stachybotrys* spores as well as hyphal fragments can cause inflammatory responses (Øya et al. 2018), meaning that the entire fungus (spores and mycelium) is harmful. Lastly, *Stachybotrys chartarum* can produce a series of volatile organic compounds (VOCs) (Wilkins et al. 2003; Betancourt et al. 2013) when growing in our buildings and mycologists working with pure cultures of *Stachybotrys* attribute any rashes or bleeding noses to the VOCs. Whether these volatile metabolites contribute to or even cause the negative health effects that some occupants of mouldy buildings experience is, as in Multiple Chemical Sensitivity, one of the most urgent questions now in indoor climate research.

Future problems due to Stachybotrys

With more than 97% of US homes built with gypsum board (Gypsum Association 2018) and a higher frequency of extreme weather (stronger hurricanes and torrential rain), *Stachybotrys* will continue to grow and thrive in our homes. The same trend is seen in Europe and since much of the paper for gypsum wallboard comes from recycled cardboard—often stored outside for longer periods in all weather—the problem will continue to grow. The Tropics might suffer the same problem, if Western building habits and materials (i.e. the use of gypsum wallboard made from recycled cardboard) are adopted. Very little effort and research is being put into the control of indoor fungal growth. In Europe fungicides are not an option, since homeowners demand houses made from natural and sustainable products and materials. So, as always, the best approach is prevention, which means securing against water ingress and severe condensation. In conclusion, *Stachybotrys* is an altogether unwelcome lodger that should be evicted as quickly and carefully as possible.

7. Amanita phalloides: a deadly mushroom

How Amanita phalloides is one of the most poisonous mushrooms

The Death Cap *Amanita phalloides* is one of most lethal mushrooms and has probably killed thousands of people throughout the history (Fig. 11). Dosages of 30 grams (approximately half of a mushroom) can kill an adult human (Bergis et al. 2012; Thongbai et al. 2017). The toxicity is not inactivated by heating or drying the mushrooms. This dangerous mushroom is the type species of *Amanita* section *Phalloideae*, one of seven sections of the genus *Amanita,* which contains all of the deadly poisonous species. Currently almost 60 species are recognized in the section (http://

Fig. 11 **a** Fruiting bodies of *Amanita phalloides*, immature, **b** mature. Photo credits: Benjarong Thongbai (**a**) and Harry Andersson (**b**), in Germany

www.amanitaceae.org/?section%20Phalloideae, Tulloss and Yang 2018), among which *A. bisporigera*, *A. verna* and *A. virosa* are known as the "Destroying Angels".

Distribution

Amanita phalloides is widely distributed across Europe, North America's East and West Coasts, Australia, and western Asia (northern Iran) (Pringle and Vellinga 2006; Pringle et al. 2009; Dadpour et al. 2017). In the field, the risk of unintentional poisoning is high because fruiting bodies resemble several edible species, such as immature Caesar's mushrooms in *Amanita* sect. *Caesareae* Singer ex Singer, as well as *Volvariella volvacea* (Bull.) Singer. They are also sometimes confused with edible *Russula* species. Besides *Amanita* spp. other are mushrooms contain deadly toxins, for example, *Galerina marginata* (Fr.) Kühn. and *Lepiota josserandii* Bon and Boiffard (Sgambelluri et al. 2014; Luo et al. 2015).

The chemistry

Amanita phalloides contains two types of oligopeptide toxins, which are called amanitins (Fig. 12a) and phalloidins (Fig. 12b), and have different biochemical modes of action. There are three types of amanitin: α-amanitin, β-amanitin, and γ-amanitin. Of these α-amanitin, is the major product and therefore can be regarded as the deadliest toxin Amanitins target mainly the liver and kidneys by affecting RNA synthesis via strong inhibition of eukaryotic protein RNA polymerase II, causing protein deficits and ultimately cell death. Several studies have attempted to elucidate the exact biochemical mode of action of α-amanitin, but clear conclusions have not been established (Matinkhoo et al. 2018). Interestingly, one benefit of α-amanitin has been its use as a biochemical tool, due to its selective inhibition of eukaryotic RNA polymerases, e.g. during the study of prolonged α-amanitin treatment of cells for studying mutated polymerases causes degradation of DSIF160 and other proteins (Tsao et al. 2012). The study has shown the outstanding activity of α-Amanitin in therapy-resistant tumour cells, e.g. cells expressing multi-drug resistant transporters and tumour-initiating cells (Kume et al. 2016; Matinkhoo et al. 2018).

Phalloidin, in contrast, is a strongly cytotoxic cytoskeleton inhibitor that interferes with cells by binding F-actin, preventing its depolymerization and thereby poisoning the cells. It has also been reported to inhibit adenosine triphosphate hydrolysis activity (Cooper 2007). Notably, no study has confirmed the action of phalloidin in patients, but it is very probable that the presence of two types of toxins with different biochemical modes of action further potentiates the toxicity of the mushroom.

The future

Human fatal cases continue to be reported in the media or in scientific reports. In 2015, one of three in a family was

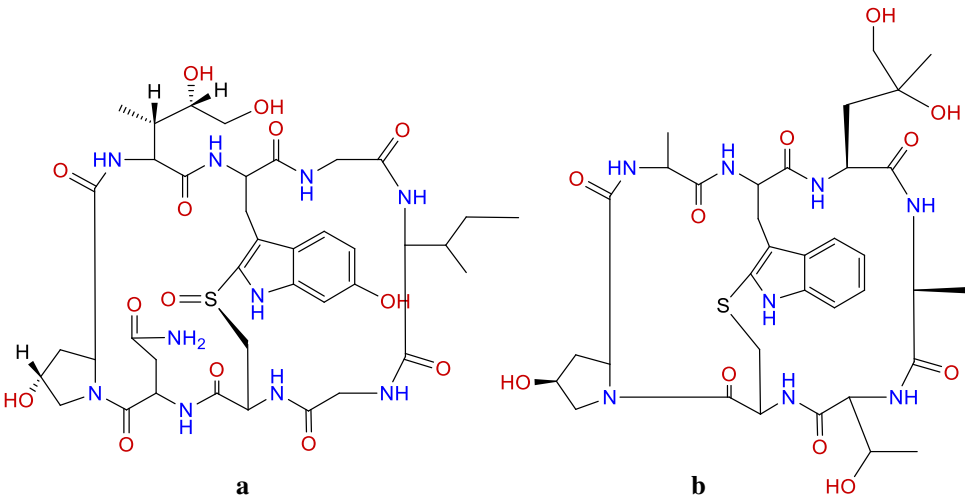

Fig. 12 Chemical structures of **a** α-amanitin and **b** phalloidin

poisoned in Poland, and several immigrants from the Middle East were poisoned with six dead in Germany. In 2014, four people in California were poisoned. Fortunately, three survived because of liver transplants (Pawlowska et al. 2006; Gardiner 2012). The symptoms of patients often do not become evident for 6–20 h. Patients suffer from abdominal pains, vomiting, and severely dehydrating diarrhoea in the early stages from 6 to 8 h. Eventually, the liver and kidneys fail to function after 24–36 h, leading to coma and death. It is surprising that *A. phalloides*, which has long accidentally poisoned people, continues to poison more and more each year. To ensure personal safety, the best recommendation is to not consume any wild mushrooms which have not been reliably identified. It is also worth noting that *A. phalloides* has a range of white-yellow-olive-green colours with volva (underground!), has no distinct odour, and can grow mixed with edible species. The number of human fatalities is much lower, when patients are able to get medical treatment as quickly as possible after consumption. Initial therapy is to check for *Amanitin-ELISA* in the urine. High doses of silibinin, penicillin, and *N*-acetyl-cysteine, all of which have large ring structures similar to the toxin, have been used as treatments in Europe but with varying success. Unfortunately, the discovery of a treatment or effective antidote is still elusive.

Damage to human dwellings and belongings

Although becoming less of a problem due to modern house constructions, the damage fungi cause to our dwellings or historic buildings by rotting wooden structures can be considerable. Therefore, *Serpula lacrymans* is chosen as an example of a serious dry rot wood decay fungus and the 8th most feared fungus. Fungi not only rot wood but also attack numerous other household items. The problem is much more acute in the tropics where high humidity encourages fungal growth and household items such as paper, books, dried food, clothes and furniture all succumb to mould.

8. Serpula lacrymans: wood decay basidiomycetes

The dry rot fungus *Serpula lacrymans* is (Fig. 13) the most damaging destroyer of wood construction materials in temperate regions and only found in a few natural environments. *Serpula lacrymans* is member of the Basidiomycota (order Boletales), a brown rot fungus causing what is commonly known as dry rot, and is one of the most destructive wood decay fungi in buildings, especially those with a high moisture content. It is sometimes referred to in common parlance as "building cancer" (Watkinson and Eastwood 2012). *Serpula lacrymans* was introduced by humans from its natural range in the mountainous tree lined habitats of the Himalayas where it invaded houses, throughout Europe, North America and Australia

Fig. 13 *Serpula lacrymans* indoor infestation of: **a** door frame, **b** panelling in a bedroom, **c** furniture, **d** fruiting body emerging from plaster work illustrating why this fungus is so successful in indoor construction by travelling through plaster work by rhizomycelium

(Balasundaram et al. 2018). As an ecological specialist, *S. lacrymans* was able to colonise the built environment due to preadapted characteristics lacking in "wild" relatives, such as intracellular transport mechanisms linked to a corded mycelial network (Balasundaram et al. 2018). Despite being a widespread destroyer of indoor timber construction, it is rarely found outside invaded houses beyond its natural range. It thrives in poorly ventilated, dark places with elevated moisture levels and spreads through masonry, causing structural damage. *Serpula lacrymans* spreads by thick mycelial rhizomorphs which aids in the movement of water, nitrogen, iron and in the secretion of hydrolytic cellulases and oxidative enzymes for the breakdown of cellulose in wood. *Serpula lacrymans* is less likely to cause problems in modern buildings because it requires relatively damp wood and very high relative humidity for growth. However, the increasing use of timber and non-standard construction materials could provide a new niche for the fungus in the future. The optimum temperature for growth and spread of *S. lacrymans* is around 20–22 °C and a moisture content of 30–40% (Gabriel and Švec 2017).

Species involved in wood rot

Serpula lacrymans is among a group of basidiomycetes that causes brown rot of timber as it utilises the cellulose and hemicellulose, without the total decomposition of lignin. This results in brown colouration of the infected wood, which breaks up forming the "cubical cracking" that is typical of brown rot attack, eventually the wood turns to a powdery brown lignin residue. The mechanism of decay is

proposed to occur through an initial non-enzymatic disruption of the dense lignocellulose structure by hydroxyl radicals generated via a chelator-mediated Fenton system (Goodell et al. 2017). After hydrolysis of cellulose and hemicellulose follows the activity of degradative enzymes that are then able to penetrate the disrupted substrate (Presley and Schilling 2017). This mechanism is supported by genome analyses of brown rot species including *S. lacrymans* which have shown a refinement in specific decay enzymes, e.g., the loss of class II peroxidases and some endocellulases, while certain groups of cellulases and pectinases are increased (Floudas et al. 2012). Dry rot caused by *S. lacrymans* can be confused by non-professionals with other similar brown rot decay species, such as *Fibroporia (Antrodia) vaillantii and Coniophora puteana,* which also may attack timber in buildings. Other brown-rot fungi that may damage housing include *Donkioporia expansa*, *Phaeolus schweinitzii*, *Postia placenta*, *Gloeophyllum trabeum* and *Fomitopsis pinicola. Serpula lacrymans* these days is of greatest concern in old or historic buildings where timber is subject to water ingress and wood is untreated (Frankl 2014; Kazartsev et al. 2014). Gabriel and Švec (2017) listed the species abundance of seven indoor wood decay basidiomycetes reported in Europe in which *S. lacrymans* was the most frequent, with *Coniophora puteana* second.

Treatments

Various treatment options are available: (1) Identify and replace decayed wood, (2) Replace all timbers, (3) Treatment with biocides, and in all cases treatment of the surrounding masonry may also be advisable. After treatment it is important to improve the ventilation and increase air flow to dry the surrounding masonry. Present day timbers are variously treated with wood preservatives thus avoiding remedial treatment which can be expensive. The cost of remedial treatment or prevention is difficult to ascertain as these are often one-off events (Gabriel and Švec 2017). However, the following are examples: *Serpula lacrymans* is the cause of many millions of USD damage each year (Palfreyman 1995); in France, annually it costs 30 million Euros to treat wood decay damage (Maurice et al. 2011) while in the UK, repair costs to timber in construction was £3 million per week (Rayner and Boddy 1988). Krzyzanowski et al. (1999) estimate the cost of dry rot remediation business in the UK to be in the order of £400 million.

Serpula lacrymans in closed unventilated buildings may give off a characteristic "mushroomy odour" or a strong musty smell but no allergen specific compounds have been reported so far from the fungus.

Distribution

Serpula lacrymans is mainly a problem in temperate countries and accounted for 61.5% of damages in Austria, followed by *Antrodia* spp. (10.7%) and the genera *Gloeophyllum* (8.2%), and *Coniophora* (3.9%) (Buzina, unpublished data). Ryvarden (1993) opines that although brown rot species are scattered over many systematic groups, there are very few genera that are restricted to the tropics. *Serpula lacrymans* has a maximum growth at 19–21 °C and does not tolerate high temperatures (Jennings and Bravery 1991), which probably explains its absence from the tropics and regions with high summer temperatures (Kauserud et al. 2007). The typical variety of *Serpula lacrymans* var. *lacrymans* has moved through China (Himalaya) and into Japan and is found throughout Japan. A second variant moved through Europe into the USA and Australia and then onto New Zealand, but again is only really associated with temperate regions (Kauserud et al. 2007). The wild relatives (*S. himantioides*, *S. lacrymans* var. *shastensis,* Himalayan-native of *S. lacrymans* var. *lacrymans*) are exclusively temperate/high altitude montane specialists. Kauserud et al. (2007) suggest there is very low genetic variation in the founder populations indicating a comparative recent origin with infection of wood materials transported over land or sea.

Plant and forest pathogens

Plant pathogens present very important problems which should be feared. Field crops, cereals and horticultural crops are attacked by many different pathogens (including fungi) and insects. Some pathogens may have devastating effects on yield and quality, causing major diseases such as wheat rust and rice blast, among many others. However, forest diseases can also cause considerable economic losses and some may result in major environmental disturbance affecting forest composition, forest health, and even the animals living in the forest.

The entry of tree pathogens to Australia, Great Britain, New Zealand, the USA and numerous other countries in recent years is alarming. Serious pathogens include *Hymenoscyphus*, *Fusarium* and *Phytophthora* species, but myrtle rust, which has recently entered Australia and New Zealand with devastating consequences, is chosen as our 9th most feared fungus.

9. Austropuccinia psidii: an invasive rust fungus with an extremely broad host range

Austropuccinia is a monotypic genus described by Beenken (2017) for the rust fungus now commonly known as myrtle rust, *A. psidii*. The fungus was first described in 1884 as *Puccinia psidii* on guava (*Psidium guajava*) in Brazil, and for a long time the disease was known as guava rust. However, somewhat unusual for a rust fungus, *A. psidii* has an extensive host range, parasitizing about 70 genera and

450 species of *Myrtaceae* (Carnegie and Giblin 2018). Myrtle rust is therefore a more descriptive moniker for this disease.

Hosts and distribution

Austropuccinia psidii attacks young, actively-growing leaves and shoot tips, and young stems. Numerous pustules (uredinia) erupt from infected parts and produce copious, wind-dispersed yellow urediniospores (Fig. 14). For instance, the regrowth of a trimmed *Lophomyrtus* hedge consisting of soft tissues was particularly susceptible to infection (Fig. 15). Uredinia can also be produced on fruits and flowers, and this is of concern to growers of feijoa fruit (*Acca sellowiana*). Symptoms can vary, depending on the host species, but in severe cases, repeated defoliation and/or dieback can lead to death of plants. Myrtle rust is an extremely invasive pathogen. Particularly during the first two decades of the 21st century the fungus has moved outside of its native area of Brazil (and probably surrounding countries) and has markedly extended its geographic range to Florida (1977), Mexico (1981), Hawaii (2005), Japan (2007), China (2009), Australia (2010), South Africa (2013), New Caledonia (2013), Indonesia (2015), New Zealand (2017), and throughout Central and South America (Carnegie and Giblin 2018). Strict measures put in place in Hawaii, Australia and New Zealand following introduction of the rust invariably failed to prevent its establishment and further spread.

The host family *Myrtaceae* is particularly abundant in Australia and tropical America, with over half of all species being native to Australia. Some members of direct economic importance for forestry and fruit production include *Eucalyptus* spp., feijoa, guava, and rose apple (*Syzygium* spp.); spices derived from the family include allspice (*Pimenta dioica*) and clove (*Syzygium aromaticum*); other species are cultivated in nurseries as ornamental plants (e.g., *Lophomyrtus*); while bay rum oil is extracted from *Pimenta racemosa* and lemon myrtle oil from *Backhousia citriodora*. Tea tree species (*Leptospermum* and *Kunzea*) are important cover plants in forest re-establishment and also an important nectar source for bees in the production of honey. Many members of the family are environmentally and ecologically important members of the natural vegetation (e.g. *Merosideros* spp. in Hawaii and New Zealand), and in Australia some species of endangered native trees are under threat of extinction through dieback and repeated rust infections (Carnegie et al. 2016; Carnegie and Pegg 2018). In the 1970s, *Eucalyptus* rust (as it was also known) became a dominant threat to plantations of introduced *Eucalyptus* in Brazil; it caused large-scale losses in nurseries and in young plantations (Coutinho et al. 1998).

Taxonomy

Several authors (e.g., Graça et al. 2011; Sandhu et al. 2016) assume that the myrtle rust is a species complex; future research will show how many species exist in the genus.

Fig. 14 Close up of myrtle rust (photo credit: Dr. Grant Smith)

Fig. 15 Myrtle rust infection on soft new growth of a recently trimmed hedge of the New Zealand endemic plant, *Lophomyrtus obcordata.* Despite an extensive advertising programme and the hedge being beside a footpath, the infection was seen by a botanist, and was not reported by the public

Presently, only one strain occurs in Australia and New Zealand, but several strains have been identified elsewhere (Furtado and Marino 2003; Graça et al. 2011). *Austropuccinia*, literally meaning 'southern *Puccinia*' is phylogenetically distinct from the genus *Puccinia* (Tan et al. 2014; Beenken 2017), despite both genera having morphologically similar two-celled teliospores. *Puccinia* belongs to family *Pucciniaceae*, while *Austropuccinia* is placed in family *Sphaerophragmiaceae* along with other genera such as *Dasyspora*, *Puccorchidium*, *Sphenorchidium* and *Sphaerophragmium*.

Ecology

As with most rust pathogens, myrtle rust is well adapted for aerial dispersal by wind, but it can also be transported on clothing, equipment, live plants, bees etc. It is not known specifically how it spreads over a wide area of the globe, but some long-distance movement has undoubtedly been through live plant trade (Grgurinovic et al. 2006). However, in April 2017, myrtle rust was discovered on *Metrosideros kermadecensis* trees in Kermadec Islands, a remote group of islands 1000 km north-east of New Zealand; this find followed the path of an ex-tropical cyclone from eastern Australia. About 1 month later, the rust was also found on mainland New Zealand, following the north–south movement of another ex-cyclone. Being first found in eastern Australia (New South Wales) in 2010 it rapidly spread and by 2015 had reached as far south as Tasmania and northwards to the Northern Territory.

Why myrtle rust is a threat?

Myrtle rust is of major concern for Australia; most of its native ecosystems are dominated by plants in the Myrtaceae family. There are more than 2200 native myrtaceous species in Australia, of which about 350 species have been determined as hosts. About 45 species are highly susceptible, and two of these have had their threat classification raised to critically endangered. Repeated infections and dieback will eventually lead to branch dieback and tree death, and also open the canopy to light, which may affect other plant species. In New Zealand, *Metrosideros excelsa* (New Zealand Christmas tree) produces a brilliant display of red flowers near Christmas; possible long-term effects of myrtle rust on this species are unknown. Likewise, in Hawaii, the threat of myrtle rust to the culturally significant *M. polymorpha* ('ōhi'a) is of major concern. It appears as though native ecosystems in warmer parts of Australia are invaded, whereas in cooler regions it is plants in gardens that are infected. To date, in New Zealand, it is cultivated plants that have been most impacted.

Other forest pathogens

Besides myrtle rust there have been several forest pathogens on the move which have caused serious problems to forestry in the respective countries entered. For example, *Agathis australis* (kauri) grows in the far north of New Zealand and is considered to be a national treasure. The largest remaining tree is the iconic "Tāne Mahuta" (Lord of the Forest). This tree is up to 2500 years old and in size is second only to the giant Californian redwood trees, *Sequoiadendron giganteum* and *Sequoia sempervirens*. In 2006 a disease was reported from kauri and it has since spread to most kauri forests. The disease is caused by the oomycete pathogen *Phytophthora agathidicida* (Weir et al. 2015), and is now commonly referred to as kauri dieback, but kauri death is the usual outcome (Fig. 16).

Phytophthora agathidicida is soil borne and the main means of dispersal is almost certainly humans carrying infested soil on their footwear. It is estimated that thousands of trees are infected, and long-term survival of kauri forests cannot be guaranteed. Many walking tracks have been closed to the public in order to help prevent spread of the pathogen. It is not known if any of the other species of *Agathis* in Australasia, or parts of south-east Asia, are susceptible (or resistant) to *P. agathidicida.* It seems unlikely that *P. agathidicida* is native to New Zealand, but many questions remain. How did the organism get to New Zealand and when did it arrive? Where did it come from? Does it infect other plant species in New Zealand? Does it infect *Agathis* species in any of the nearby countries? Will kauri become extinct within the next few decades? The final question is a frighteningly possible scenario.

When a novel pathogen enters a new country the effects may be devastating, altering the landscape drastically and affecting the habitats of numerous animals. Those plant pathogens that infect commercially grown crops may be economically damaging for a country. For this reason quarantine plays an important role in keeping out pests and diseases. The most important plant diseases were presented by Dean et al. (2011). However, this list included only agricultural pathogens and no such list has been prepared for forest pathogens. In Table 1 we provide a list of some invasive forest pathogens that are currently spreading, the problems they cause and the countries affected.

Animal pathogens

Although generally less feared unless infecting the pet dog or cat, animal pathogens can have devasting consequences on animal populations worldwide. *Batrachochytrium dendrobatidis* is probably the most serious example where an

Fig. 16 **a** Dying *Agathis australis* tree at advanced stage of canopy decline following infection with *Phytophthora agathidicida*; the clumps of green are epiphytes (photo credit: R.E. Beever), **b** Gummosis on base of *Agathis australis* tree following infection with *Phytophthora agathidicida* (photo credit: S.E. Bellgard)

Table 1 Some recent serious, invasive forest diseases (in alphabetical order and including both fungi and oomycetes)

Taxon	Problem	Countries or regions affected
Austropuccinia psidii	An invasive rust fungus with an extremely broad host range	Australia, Brazil, Florida, Hawaii, Indonesia, Japan, Mexico, New Caledonia, New Zealand, South Africa
Bretziella fagacearum = *Ceratocystis fagacearum*	Oak wilt	USA
Ceratocystis lukuohia (destroyer of ‘ōhi’a) is the more agressive fungus; *C. huliohia* (disruptor of ‘ōhi’a) is the less agressive fungus.	Rapid Ohi’a death, Hawai’i’s most abundant native tree	Hawaii
Cronartium ribicola	White pine blister rust	China, North America
Fusarium circinatum	Pine pitch canker	Chile, Japan, Mexico, South Africa, Spain, USA
Hymenoscyphus fraxineus	Ash dieback	Europe
(= *Chalara fraxinea, Hymenoscyphus pseudoalbidus*)		
Ophiostoma novo-ulmi	Dutch elm disease	Europe, North America
Phytophthora agathidicida	Kauri dieback	New Zealand
Phytophthora austrocedri	Chilean cypress mortality	Argentina
Phytophthora cinnamomi	Phytophthora dieback, jarrah dieback	Australia
Phytophthora ramorum	Sudden oak death	California
Raffaelea lauricola	Laurel wilt	USA
Raffaelea quercivora	Japanese oak wilt	Japan

animal pathogen is wiping out entire species and populations of amphibians and is therefore included as our 10th most feared fungus.

10. Batrachochytrium dendrobatidis

The Chytridiomycota (chytrids) was once an obscure phylum of fungi that seemed unlikely to be of much ecological importance and had few specialists with knowledge of the group. As well as being saprobes, many chytrids are pathogens of algae and various protozoans, and a few are pathogens of plants (Karling 1964). None, however, had been reported as a pathogen of vertebrates. Following years of widespread reports of enigmatic declines of frog populations (e.g., Laurance et al. 1996; Stuart et al. 2004), a chytrid fungus was recognized as the pathogen causing chytridiomycosis, a lethal disease of amphibians (Berger

et al. 1998). The fungus, named *Batrachochytrium dendrobatidis* (Longcore et al. 1999), is classified in the Order Rhizophydiales in the Phylum Chytridiomycota. As with most other chytrids, *B. dendrobatidis* reproduces asexually via motile spores (zoospores). The tiny ($\sim$ 5 µm diameter) zoospores (Fig. 17a) swim with a posteriorly directed flagellum; with no cell wall zoospores do not survive drying and thus the organism requires aquatic conditions to disperse. Morphologically, *B. dendrobatidis* consists of a more or less sphaerical, chitin-walled thallus from which rhizoids extend into the substrate (Fig. 17b, d) (Longcore et al. 1999). In pure culture the time to develop from zoospore to release of zoospores (Fig. 17a–f) is about 4 days with an optimum temperature range of 15–25 °C. Isolates cease growth and ultimately die at 28 °C (Piotrowski et al. 2004; Voyles et al. 2017). Unlike most other chytrids, *B. dendrobatidis* sometimes develops multiple zoosporangia (colonial thalli) from a single zoospore (Figs. 17c, 18) (Berger et al. 2009). Neither sexual reproduction nor resting spore formation has been seen for *B. dendrobatidis*, however, hybrid lineages have been reported, indicating that recombination exists (Schloegel et al. 2012; O'Hanlon et al. 2018).

The disease and hosts

Chytridiomycosis, caused by *Batrachochytrium dendrobatidis* is a skin disease with a broad host range, infecting keratinized mouthparts of amphibian larvae and adult skin of all three orders of Amphibia: Anura (frogs and toads), Urodela (salamanders), and Apoda (caecilians) (Gower et al. 2013). The degree of infection varies, from a few thalli growing in skin cells of the foot area to extensive infections that cover much of the epidermis—disrupting skin function, interfering with electrolyte transfer, and ultimately causing death (Voyles et al. 2009). Early researchers determined infection status by microscopy of living or stained adult skin (particularly of the feet and legs) or larval mouthparts (Fellers et al. 2001); now, however, non-invasive PCR techniques enable diagnosis from DNA collected in the field by swabbing the epidermis (Annis et al. 2004; Boyle et al. 2004). *Batrachochytrium dendrobatidis* DNA also can be detected from environmental samples (Kirshtein et al. 2007), theoretically enabling detection of the chytrid before frogs begin to die (Kamoroff and Goldberg 2017). Besides different species of amphibians varying in their susceptibility to infection, infection rates vary in different habitats, with species in montane areas of Australia, Central America, western North America, and Spain being particularly susceptible to population declines (Berger et al. 1998; Bosch et al. 2001; Fellers et al. 2001; Muths et al. 2003; Lips et al. 2006). In contrast to montane areas, elevated temperatures as found in lowland tropical regions, can control infection and are probably effective in maintaining amphibian populations in warmer areas (Berger et al. 2004; Greenspan et al. 2017).

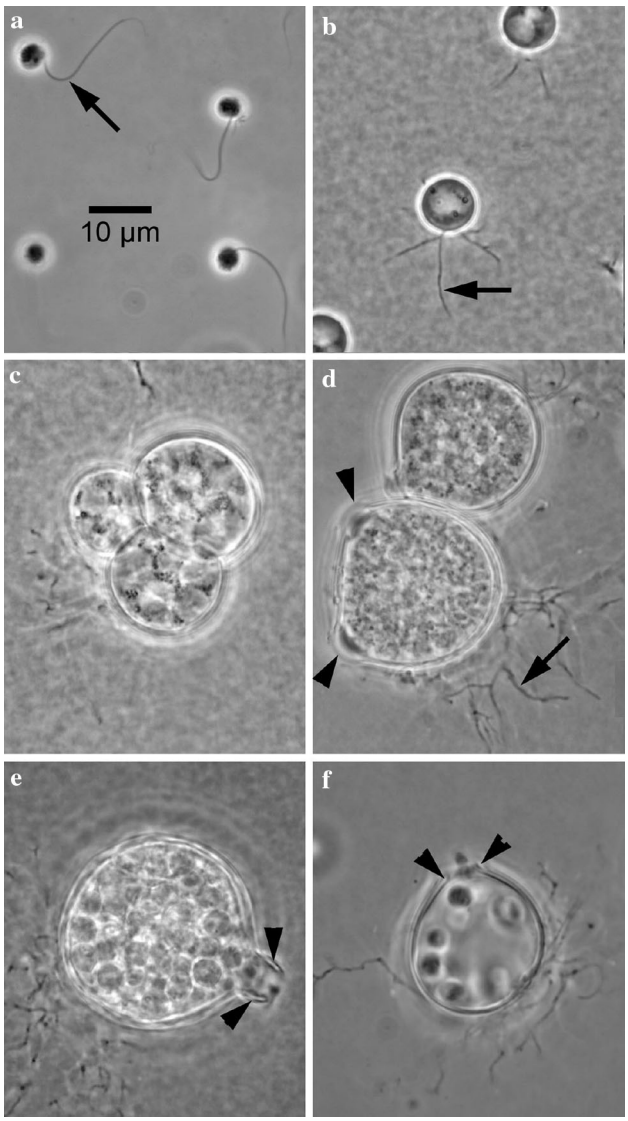

Fig. 17 Development of *Batrachochytrium dendrobatidis* on 1% tryptone nutrient agar. **a** Zoospores; arrow indicates flagellum. **b** One-day old developing thallus; arrow indicates rhizoid. **c** A few sporangia develop colonially (more than one thallus from a single zoospore). **d** Three-day old thalli; arrowheads point to developing discharge papillae; arrow indicates rhizoid. **e** Four-day old thallus; arrowheads indicate open discharge papilla. **f** Zoospores exiting sporangium; discharge papillae may be long or short (arrowheads). Magnification bar in **a** for all figures

Although *B. dendrobatidis* grows inside of keratinized skin cells of amphibians, its ability also to grow in pure culture (Longcore et al. 1999; Fisher et al. 2018) has enabled a vast amount of research over the last 20 years, greatly increasing knowledge of its enzymatic capabilities enriched in proteases (Rosenblum et al. 2008; Joneson et al. 2011; Farrer et al. 2017), its phylogenetic placement (James et al. 2006), and its intraspecific lineages (Bataille

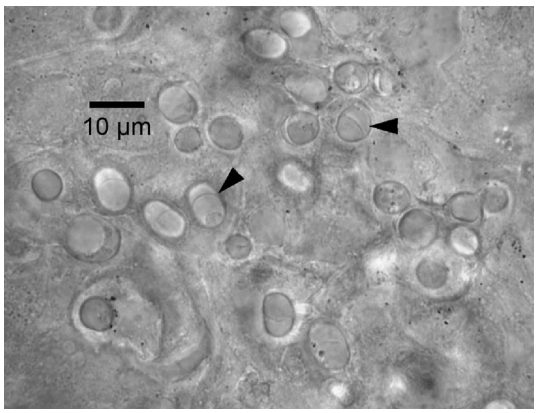

Fig. 18 Light microscopic, unstained view of *Batrachochytrium dendrobatidis* infection in foot epidermis of green frog (*Lithobates clamitans*); arrowheads indicate colonial thalli

et al. 2013; Jenkinson et al. 2016; O'Hanlon et al. 2018). Previously it was understood that chytrids were haploid in their vegetative state (e.g., Alexopoulos et al. 1996; Doggett and Porter 1996), however, *B. dendrobatidis* is usually diploid and chromosome copy numbers may range from 2 to 5, with not all chromosomes in an isolate having the same copy number (Farrer et al. 2013; Rosenblum et al. 2013).

Batrachochytrium dendrobatidis was at first thought to be a single, recently emerged clone (Morehouse et al. 2003), but with more advanced methods and an increasing number of available cultures, different strains of *B. dendrobatidis* have been found. Endemic strains occur in Africa, Asia, Europe, and South America (Schloegel et al. 2012; Bataille et al. 2013; Farrer et al. 2013). The predominant strain in most areas, however, is the Global Panzootic Lineage (Bd-GPL), which seems to be more pathogenic than the endemic lineages (e.g., Greenspan et al. 2018). This lineage is truly global, being found on all continents that have amphibians. Since the discovery that *B. dendrobatidis* was decimating amphibian populations, scientists have been trying to determine where the disease originated and why it has suddenly emerged. *Batrachochytrium dendrobatidis* has been isolated from amphibians around the world and DNA markers and whole genomes have been analysed. Analyses of nuclear genomes and mitochondrial DNA indicate that the Korean Peninsula is the most likely site of *B. dendrobatidis* origin (O'Hanlon et al. 2018). It appears that Bd-GPL emerged between 120 and 50 years ago (O'Hanlon et al. 2018)—the era of increasing intercontinental trade in amphibians, particularly the North American bullfrog, which is a carrier of *B. dendrobatidis* but usually does not die from the infection (e.g., Greenspan et al. 2012; Yap et al. 2018).

Batrachochytrium salimandravorans, a sister species of *B. dendrobatidis,* was described in 2013 (Martel et al. 2013b). *B. salimandravorans* differs from *B. dendrobatidis* in its slightly different developmental morphology (zoospore cysts germinate with a germ tube even in pure culture, whereas those of *B. dendrobatidis* do not); its zoospore cysts appear to act as thin-walled spores; it has a lower temperature optimum; its host range is primarily limited to salamanders; and its growth in skin cells causes erosive lesions. *Batrachochytrium salimandrivorans* is endemic in Southeast Asia where it does not kill its hosts but in Denmark and Belgium it has caused die-offs of European fire salamanders (Martel et al. 2013a).

Why should the disease be feared?

Some authors suggest that Earth is in the middle of the sixth great extinction (e.g., Wake and Vredenburg 2008) and amphibians are unduly affected. Loss of species is beyond monetary consideration; the real cost of *B. dendrobatidis* is to the ecosystem (e.g., Hocking and Babbitt 2014) and is incalculable. Monetary concerns do, however, affect decisions made about international and even within nation trade. The North American bullfrog is farmed for food on several continents and is implicated as one of the inter-continental carriers of *B. dendrobatidis*; amphibians transported for the pet trade and for scientific purposes also carry the fungus (e.g., Schloegel et al. 2009; Gratwicke et al. 2010; Gerson 2012). To protect amphibian species from extinction zoos and projects such as the Panama Amphibian Rescue and Conservation Project, concentrate efforts and resources on maintaining assurance colonies of amphibians susceptible to *B. dendrobatidis* (e.g., Gagliardo et al. 2008). Costs are also incurred in *B. dendrobatidis* research. A *Google Scholar*® search for scientific papers between 1999 and 2018, with "*Batrachochytrium*" and "chytridiomycosis" as search terms, returned 4590 results. When ordered by relevance, the first 1000 scientific papers were still primarily about *B. dendrobatidis*, indicating the large amount of time and research funds that have gone into studying this fungus.

Distribution

The worldwide distribution of *B. dendrobatidis* and the recent spread of *B. salimandravorans* out of Asia are particularly disturbing because members of the whole Class Amphibia rather than a single genus or species can be affected. The discovery of hybrid lineages (Schloegel et al. 2012; O'Hanlon et al. 2018) means that recombination has taken place in *B. dendrobatidis* several times; the invasive Bd-GPL may itself have arisen from a hybridization event (Farrer et al. 2011). Continued distribution of *B. dendrobatidis* via amphibian trade means that different *B. dendrobatidis* lineages will inevitably come into contact and a new hybrid lineage may arise, possibly with a greater temperature tolerance or host range than Bd-GPL.

Batrachochytrium dendrobatidis is present in 52 of 82 countries from which sampling has been reported (Olson et al. 2013). The online interactive world map that is a part of the *B. dendrobatidis* mapping project (http://www.B.dendrobatidis-maps.net/maps/) gives specifics for location, host species and other data. The pattern of die-off events seems to have moved through Central America, Eastern Australia and Spain leaving reduced population numbers and diversity. *Batrachochytrium salimandrivorans*, however, has more recently been spread out of Asia into Europe and its absence in North America, which is a hotspot of salamander diversity, relies on observance of new trade rules. A few frog populations have recovered after severe declines; however, recovery seems to be because of changes in the amphibians rather than a decrease in the virulence of *B. dendrobatidis* (Knapp et al. 2016; Voyles et al. 2018). Not discussed here, but pertinent to the future of amphibian populations and their interaction with *B. dendrobatidis* and *B. salimandrivorans* is that human activities that result in habitat alteration remain major drivers of reduced amphibian populations (Wake and Vredenburg 2008). Because amphibian species that carry only slight infections exist in most areas, *B. dendrobatidis* can remain at low background levels. Preserving diverse amphibian habitats will give the best chance for host evolution and recovery (DiRenzo et al. 2018).

Combatting the disease

In attempts to find methods to combat frog deaths caused by *B. dendrobatidis*, pure cultures have been co-cultured with frog-produced antimicrobial peptides (e.g., Rollins-Smith and Conlon 2005) and epidermal bacteria (e.g., Harris et al. 2009). Some of these bacteria and compounds affect growth of *B. dendrobatidis* in vitro and in vivo; however, means to convert this information into control at the environmental level are lacking. Commercial antifungals such as itraconazole are effective in controlling growth of the fungus in contained situations (e.g., Nichols and Lamirande 2001) and their use has led to successful treatment of captive, infected frogs (e.g., Brannelly et al. 2012). Although *B. dendrobatidis* is now distributed throughout much of its potential range, the possibility that mixing of strains could produce a new hybrid with enhanced pathogenicity or greater temperature tolerance means that importation laws need to be passed, enhanced, and enforced (Lips 2018). Importation laws are particularly important to prevent further spread of *Batrachochytrium salimandrivorans* from Asia and Europe.

The effects of Bd-GPL on all amphibian-inhabited continents and *B. salimandrivorans* in Europe remind us that we, as societies, have a responsibility to safeguard our biota during this current rapid globalization as international trade and other human activities are leading to the spread of pathogenic fungi. In North America chestnuts, elms, oaks, beech trees and other beloved and important plant components of the natural ecosystem have been ravaged by fungi not native to the continent. These fungi and *B. dendrobatidis* were not intentionally imported, but because fungal hyphae and spores are microscopic they easily travel in and on imported goods. Even with rules and inspections, not every shipment can be monitored. That intercontinental movements of pathogens continue to happen, in spite of regulations, means that we can expect more fungal invasions to occur as our world continues to become more globalized.

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Affiliations

Kevin D. Hyde[1,2] · Abdullah M. S. Al-Hatmi[3,6] · Birgitte Andersen[4] · Teun Boekhout[5,6] · Walter Buzina[7] · Thomas L. Dawson Jr.[8,9] · Dan C. Eastwood[10] · E. B. Gareth Jones[12] · Sybren de Hoog[6,11] · Yingqian Kang[13] · Joyce E. Longcore[14] · Eric H. C. McKenzie[15] · Jacques F. Meis[11,16] · Laetitia Pinson-Gadais[17] · Achala R. Rathnayaka[2] · Florence Richard-Forget[17] · Marc Stadler[18] · Bart Theelen[6] · Benjarong Thongbai[18] · Clement K. M. Tsui[19,20]

[1] Key Laboratory for Plant Diversity and Biogeography of East Asia, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, Yunnan, People's Republic of China

[2] Center of Excellence in Fungal Research, Mae Fah Luang University, Chiang Rai 57100, Thailand

[3] Ministry of Health, Directorate General of Health Services, Ibri, Oman

[4] Department of Biotechnology and Biomedicine, Technical University of Denmark, 2800 Kgs. Lyngby, Denmark

[5] Institute for Biodiversity and Ecosystem Dynamics (IBED), University of Amsterdam, Amsterdam, The Netherlands

[6] Westerdijk Fungal Biodiversity Institute, Utrecht, The Netherlands

[7] R&D Institute for Hygiene, Microbiology and Environmental Medicine, Medical University Graz, Neue Stiftingtalstrasse 6, 8010 Graz, Austria

[8] Institute for Medical Biology (IMB), Agency for Science, Technology, and Research (A*STAR), Singapore, Singapore

[9] Departments of Drug Discovery and Biomedical Sciences and Biochemistry and Molecular Biology, Center for Cell Death, Injury and Regeneration, Medical University of South Carolina, Charleston, SC, USA

[10] Department of Bioscience, Academic Office, 102, First Floor, Wallace Building, Swansea University, Singleton Campus, Swansea, Wales, UK

[11] Centre of Expertise in Mycology Radboudumc/Canisius Wilhelmina Hospital (CWZ), Nijmegen, The Netherlands

[12] Portsmouth, Hampshire PO5 3DH, UK

[13] Department of Microbiology and the Key Laboratory of Proteomics, Guizhou Medical University, Guiyang, China

[14] School of Biology and Ecology, University of Maine, Orono, ME 04469, USA

[15] Manaaki Whenua-Landcare Research, Private Bag 92170, Auckland, New Zealand

[16] Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital (CWZ), Nijmegen, The Netherlands

[17] INRA, UR1264 MycSA, 71 av Edouard Bourlaux, 20032, 33882 Villenave D'Ornon Cedex, France

[18] Department Microbial Drugs, Helmholtz Centre for Infection Research, and German Centre for Infection Research (DZIF), Partner Site Hannover-Braunschweig, Inhoffenstraße 7, 38124 Braunschweing, Germany

[19] Department of Pathology, Sidra Medicine, Doha, Qatar

[20] Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, Ar-Rayyan, Qatar