Science of the Total Environment 851 (2022) 158284

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Review

Effectiveness of front line and emerging fungal disease prevention and control interventions and opportunities to address appropriate eco-sustainable solutions

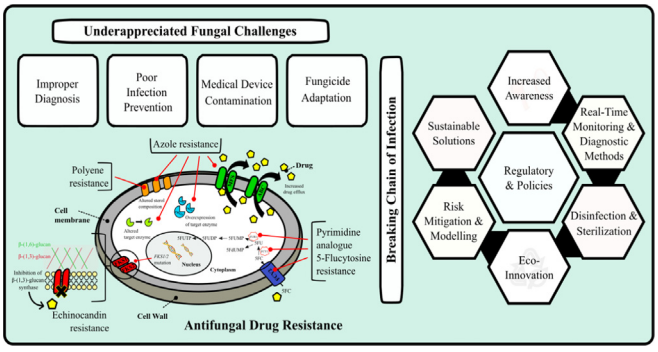
Mary Garvey [a,b], Elaine Meade [a,b], Neil J. Rowan [c,d,e,*]

[a] Department of Life Science, Atlantic Technological University, Sligo, Ireland
[b] Centre for Precision Engineering, Materials and Manufacturing Research (PEM), Atlantic Technological University, Sligo, Ireland
[c] Bioscience Research Institute, Technological University of the Shannon Midlands Midwest, Athlone, Ireland
[d] Centre for Decontamination, Sterilization and Biosecurity, Technological University of the Shannon Midlands Midwest, Athlone, Ireland
[e] Empower Eco Sustainability Hub, Technological University of the Shannon Midlands Midwest, Athlone, Ireland

HIGHLIGHTS

- Fungal infections represent an under recognised threat to public health.
- Mycosis represents high incidence of mortality.
- Antifungal resistance is increasing globally.
- New alternative eco-solutions to address pathogenic fungi are needed.

GRAPHICAL ABSTRACT



ARTICLE INFO

Editor: Damia Barcelo

Keywords:
Pathogenic fungi
Drug resistance
Environmental toxicity
Disinfection- sterilization
Sustainability

ABSTRACT

Fungal pathogens contribute to significant disease burden globally; however, the fact that fungi are eukaryotes has greatly complicated their role in fungal-mediated infections and alleviation. Antifungal drugs are often toxic to host cells and there is increasing evidence of adaptive resistance in animals and humans. Existing fungal diagnostic and treatment regimens have limitations that has contributed to the alarming high mortality rates and prolonged morbidity seen in immunocompromised cohorts caused by opportunistic invasive infections as evidenced during HIV and COVID-19 pandemics. There is a need to develop real-time monitoring and diagnostic methods for fungal pathogens and to create a greater awareness as to the contribution of fungal pathogens in disease causation. Greater information is required on the appropriate selection and dose of antifungal drugs including factors governing resistance where there is commensurate need to discover more appropriate and effective solutions. Popular azole fungal drugs are widely detected in surface water and sediment due to incomplete removal in wastewater treatment plants where they are resistant to microbial degradation and may cause toxic effects on aquatic organisms such as algae and fish. UV has limited effectiveness in destruction of anti-fungal drugs where there is increased interest in the combination approaches such as novel use of pulsed-plasma gas-discharge technologies for environmental waste management. There is growing interest in developing alternative and complementary green eco-biocides and disinfection innovation. Fungi present challenges for cleaning, disinfection and sterilization of reusable medical devices such as endoscopes where they (example, *Aspergillus* and *Candida* species) can be protected when harboured in build-up biofilm

* Corresponding author at: Bioscience Research Institute, Technological University of the Shannon Midlands Midwest, Athlone, Ireland.
E-mail address: neil.rowan@tus.ie (N.J. Rowan).

http://dx.doi.org/10.1016/j.scitotenv.2022.158284
Received 17 July 2022; Received in revised form 21 August 2022; Accepted 21 August 2022
Available online xxxx

from lethal processing. Information on the efficacy of established disinfection and sterilization technologies to address fungal pathogens including bottleneck areas that present high risk to patients is lacking. There is a need to address risk mitigation and modelling to inform efficacy of appropriate intervention technologies that must consider all contributing factors where there is potential to adopt digital technologies to enable real-time analysis of big data, such as use of artificial intelligence and machine learning. International consensus on standardised protocols for developing and reporting on appropriate alternative eco-solutions must be reached, particularly in order to address fungi with increasing drug resistance where research and innovation can be enabled using a One Health approach.

Contents

1. Introduction

Fungi represent one of the most diverse groups of organisms on the planet with an essential role in ecosystem processes and functioning (Hyde, 2022). The numbers of fungi have always been an intriguing topic; however, 150,000 innocuous, beneficial and harmful fungal species have been described to date enabled by using new DNA sequencing technologies. Despite the fact that problematical fungi infect billions of people annually, there is a significant under appreciation of their aetiological contribution to worldwide diseases (Bongomin et al., 2017). Fungal infections are a significant contributor to sepsis that has increased by 200 % in the United States since 1991 (van der Poll et al., 2017), and is the second most common pathogen to cause cancer related infections (Lortholary et al., 2017). Invasive fungal infections (IFIs) have increased with the widespread use of broad-spectrum antibiotics, immunosuppressive agents, antineoplastic drugs, and in-depth development of organ transplantation, and various invasive diagnostic techniques. *Candida*, *Aspergillus*, *Pneumocystis*, and *Cryptococcus neoformans* are the primary pathogens causing fungal infections, with *Candida* responsible for the largest number of cases, where the infection rates of *Aspergillus*, *Pneumocystis*, and *C. neoformans* have increased.

These IFIs primarily occur in patients with severe underlying diseases, malignant tumours, and other severe diseases compromising immune function and in those undergoing organ transplantation. Fungal infection termed mycosis is increasing globally in immunocompromised and immunocompetent persons, affecting 1 billion people with 1 million deaths yearly (Lass-Flörl et al., 2021). Thus, the immune status of the patient determines the severity of fungal disease, ranging from hypersensitivity, dermal infection, subcutaneous, invasive to disseminated systemic infections (Martinez-Rossi et al., 2018). *Candida* for example, is one of the most common fungal pathogens causing nosocomial bloodstream infections (BSI) or fungemia having a mortality rate of 30–40 % despite an availability of therapeutic options (Galia et al., 2022). Fungal therapeutics consist of 4 classes of antifungal drugs: the polyenes (amphotericin B and nystatin), azoles (fluconazole, itraconazole, voriconazole, posaconazole and isavuconazole), echinocandins (caspofungin, micafungin and anidulafungin) and the pyrimidine analogue 5-flucytosine (Fisher et al., 2022). Bacteraemia and fungemia are the second leading causes of mortality in patients of end stage renal disease receiving dialysis where incidence rates of 4.7 % bacteraemia and fungemia were detected in renal disease patients (Dalgaard et al., 2016).

Fungemia and bacteraemia also lead to severe cases of sepsis in affected patients due to the presence of microbial toxins (Valencia-Shelton and Loeffelholz, 2014).

Similar to bacterial pathogens, fungal pathogens are also displaying alarming rates of antimicrobial resistance (AMR). AMR is the innate or acquired ability of a microbial species (viral, bacterial, fungal, parasitic) to resist antimicrobial therapy, where biocidal resistance is also common amongst AMR pathogens (Meade et al., 2021a, 2021b, 2021c). AMR relates to molecular mechanisms of resistance including efflux pumps, degradative enzymes, target and drug modification, alterations in membrane permeability, biofilm formation and spores (Meade et al., 2021c). Efflux pumps associated with the ATP binding cassette (ABC) transporter superfamily are commonly associated with azole resistance in many fungal species (Nagy et al., 2021). While AMR is a naturally occurring event, the industrial production and mass use of antimicrobials in clinical, veterinary and food production has proliferated the issue beyond measure, making antimicrobials a non-renewable resource. Antifungal and biocidal resistance represents a significant threat to the treatment, transmission, and control of fungal pathogens. Multidrug resistance (MDR) is common in fungal pathogens including *Candida albicans*, non-*albicans Candida* strains (NAC), *Cryptococcus*, *Aspergillus*, and numerous dermatophyte species. Importantly,

Table 1
Outlining antifungal drug therapy options, mode of action and resistance profile of invasive fungal pathogens to be listed as priority pathogens by the WHO.

Drug class (drugs used in clinical practice)	Mode of action	Resistant species	Resistance mechanisms	Additional considerations
Polyenes (AMP B)	Depletes membrane ergosterol (Iyer et al., 2021)	*Pneumocystis jirovecii*	Absence of ergosterol in cell membrane (Helweg-Larsen et al., 2017)	AMP B nephrotoxicity, used in combination with flucytosine, used for treatment of Mucormycosis in humans (Dannaoui, 2017)
Azoles (Triazoles, itraconazole, posaconazole, voriconazole, isavuconazole)	Block ergosterol biosynthesis	*Cryptococcus* spp. (Lee et al., 2020) *Aspergillus* spp. *Candida albicans* and NAC *Pneumocystis jirovecii*	Upregulation of the azole target gene *ERG11*, drug efflux pumps, genetic plasticity (Iyer et al., 2021), exopolysaccharide capsule, formation of large polyploid titan cells (Zafar et al., 2019) Mutations in the *cyp51A* (Romero et al., 2019) *TR34/L98H* mutation, *TR46/Y121F/T289A* mutants (Pinto et al., 2018) *ERG11* point mutations (Wiederhold, 2017), efflux pump Absence of ergosterol in cell (Helweg-Larsen et al., 2017)	Increased expression of membrane transporters and efflux pumps (CaCDR1 and CaCDR2) correlates with azole resistance in many fungal species ATP (adenosine triphosphate)-binding cassette (ABC) family and the major facilitator superfamily (MFS) of efflux pumps also confer biocidal resistance in many microbial species (Meade et al., 2021c) Posaconazole and isavuconazole used to treat Mucormycosis (Dannaoui, 2017)
Echinocandins (anidulafungin, caspofungin, micafungin)	Disrupt cell structural integrity	*Cryptococcus* spp. (Lee et al., 2020) *Aspergillus* spp. *Candida* spp. *Mucorales* spp.	Intrinsic resistance to caspofungin (Meade et al., 2021c) Efflux pumps No in vitro activity (Dannaoui, 2017)	Potent in vitro activity against *Candida* isolates resistant to fluconazole (Wiederhold, 2017) Caspofungin used in combination with clindamycin to treat *Pneumocystis jirovecii* (Li et al., 2016)
Pyrimidine analogue (flucytosine)	Antimetabolite – blocks DNA synthesis	*Cryptococcus* spp. *Candida* spp.	Alterations in capsule biosynthesis in *Cryptococcus* Mutations in *FCY1, FCY2*, and *FUR1* genes (Billmyre et al., 2020)	5-Fluorocytosine is a prodrug converted into toxic 5FU by cytosine deaminase, a fungi specific enzyme (Billmyre et al., 2020)

fungal pathogens are often also extensively drug resistant (XDR), being defined as having resistance to more than one therapeutic agent in three or more antifungal classes (Galia et al., 2022). Importantly, therapeutic failure also relates to antifungal drug properties such as drug pharmacokinetics, pharmacodynamics and drug–drug interactions (Fisher et al., 2022).

The Global Action Plan on AMR and the Global AMR Surveillance System (GLASS) aims to promote standardised AMR surveillance using patient, laboratory, and epidemiology data to analyse the global impact of AMR (World Health, 2019). While bacterial AMR is commonly accepted, GLASS also recognises fungal AMR as a growing major threat where a lack of data increases the risk to public health. Surveillance issues relating to fungal species include poor recovery from blood samples, a lack of accurate identification, lack of susceptibility testing, and a lack of species-specific antifungal breakpoints. Surveillance studies, however, have demonstrated the presence of MDR *C. albicans* and NAC isolates being resistant to more than one therapeutic agent in two antifungal drug classes (Galia et al., 2022). The threat of AMR is recognised at a global scale as having negative impacts on health and wellbeing. The WHO has called for urgent action aligned with the Sustainable Development Goals (SDGs) with AMR listed in the top 10 dangers to public health, along with climate change and global warming (Masterson et al., 2021). The AMR global action plan established by the WHO in 2015 encouraged the United Nations (UN) members to develop and implement national action plans aimed at reducing the emergence and transmission of AMR species (Dutescu, 2021). Undoubtedly, a unified and coordinated action plan is needed to combat the threat of AMR. Additionally, the WHO has called for the establishment of a fungal priority pathogen list (Table 1) to include the following species: *Candida auris*; azole-resistant *Candida* spp., azole-resistant *Aspergillus fumigatus*, *Cryptococcus neoformans*, *Pneumocystis jirovecii*, and Mucorales due to their AMR ability (World Health, 2020). As we move further into a post pandemic era, bacterial and fungal pathogens may be overlooked as medical sectors strive to develop viral vaccine and treatment regimes. Fungal pathogens, and zoonotic cross over species, however, remain an important public health consideration within the One Health approach. A One Health approach is vital to establish the impact of AMR on the Anthropocene (planet, biosphere, atmosphere) and the consequences of the rising consumption rate of antimicrobial agents. Fungal infections of sporotrichosis, histoplasmosis and chromoblastomycosis and MDR dermatophytosis remain important as zoonotic fungal pathogens. Furthermore, the impact of global warming will undoubtedly promote a rise in fungal infectious disease globally negatively impacting public health and food security (Nnadi and Carter, 2021).

2. Growing crisis of antimicrobial resistance (AMR)

AMR is directly responsible for clinical expenses, treatment failures, morbidity, mortality, and economic costs. Reports indicate AMR costs the European Union (EU) healthcare sector approximately €1.5 billion annually with estimates from The World Bank suggesting an annual gross domestic product (GDP) loss of 6.1 trillion dollars by 2050 (Nasereddin, 2021). Reports highlight the mortality of AMR with ca. 5 million deaths involving resistant bacterial species in 2019 with 1.3 million deaths directly related to AMR species (Murray et al., 2022) significantly more than tuberculosis (TB), acquired immune deficiency syndrome (AIDS) and malaria (Iyer et al., 2021). Indeed, predictive modelling studies suggest that 10 million deaths per year will occur due to AMR by 2050, globally (Hillock et al., 2022). The crisis of AMR, therefore, requires a multisectoral approach to mitigation including monitoring, surveillance, novel therapeutic options and optimal prevention and control strategies. While national and global policies have impacted antimicrobial use, studies have shown a startling 65 % increase in antimicrobial use in the period of 2000 to 2015 alone (Dutescu, 2021). Furthermore, developed countries with higher incomes have increased levels of AMR species (Kirby and Herbert, 2013) indicating the effects of neoliberalism on economic policy, the emergence of AMR and the development and production of therapeutics by profit motivated pharmaceutical companies (Dutescu, 2021). Furthermore, the

national political and economic situation impacts on the provision of healthcare and distribution of pharmaceuticals in public and private healthcare settings where the latter may prioritise financial gain over AMR stewardship (Broom et al., 2021). Indeed, in our determination to extend human life, reduce morbidity and obtain optimal healthcare, microbial species are portrayed as loathsome with their commensal and beneficial interactions often overlooked. The extensive use of antimicrobial therapy negatively impacts gastrointestinal (GIT) microbiota, resulting in dysbiosis and associated diseases (autoimmunity, cancer, mental health disorders) leading to morbidity and economic impacts which may be avoided with the absence of prolonged antimicrobial therapy resulting from AMR infections (Meade et al., 2020a). The extensive use of antimicrobial therapy, emergence and re-emergence of resistant microbes has resulted in increasing rates of nosocomial disease where clinician's repertoire of therapeutic options is greatly diminished (Meade et al., 2021a, 2021b, 2021c).

WHO reports indicate nosocomial pathogens including *Escherichia coli* and methicillin resistant *Staphylococcus aureus* frequently display resistance to 3rd generation cephalosporins and fluoroquinolones with the Gram negative *Klebsiella pneumoniae* also displaying resistance to carbapenems (Founou et al., 2017). The ESKAPE pathogens *Enterococcus* spp., *S. aureus*, *K. pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp. represent a significant risk to public health with decreasing treatment options available. Indeed, these species are classed as the most prevalent of the life-threatening pathogens isolated from 72 % of patients in clinical settings (Benkő et al., 2020). Hospital acquired infections (HAIs) or nosocomial infections involving MDR-ESKAPE pathogens are increasing (Zhen et al., 2019) particularly in immune-compromised patients in intensive care units (ICUs) due to non-communicable disease. Emerging and re-emerging pathogens are also unpredictable in their levels of AMR and rates of mortality. *Borrelia burgdorferi* the emerging causative agent of Lyme disease for example displays AMR or antibiotic tolerance (Hodzic, 2015) and is associated with increasing prevalence and chronic morbidity. Advocacy of the continued and proliferating threat of AMR has been somewhat successful, in promoting awareness, driving research, and spurring government and organizations into action, globally. There remains however, a strong focus on antibiotic resistance and bacterial pathogens with fungal species often overlooked in both clinical and in agriculture settings. Even with the evident high mortality rates of fungal infections and ubiquitous nature of mycosis, insufficient funding into the diagnosis and therapy of fungal disease has prevailed for decades (Stone et al., 2021).

2.1. Clinical relevance of fungal AMR – a major underappreciated challenge

Fungal infectious diseases are commonly classified as opportunistic or primary affecting immunocompromised and immunocompetent person respectively, either locally or systemically. Local dermal infections are typically caused by dermatophytes (requiring keratin) and *Malassezia* spp. (requiring fatty acids from host lipids) (White et al., 2014). Systemic fungal infections often involve the opportunistic *Candida*, *Aspergilla*, *Mucorale* and *Fusarium* species. With primary pathogens including *Coccidioides*, *Histoplasma*, *Blastomyces* and *Cryptococcus* causing localised lung infection followed by systemic mycosis in immune competent persons post inhalation of fungal spores. Increasing prevalence of mycosis relates to several factors including increased number of immunocompromised patients, increased longevity, affluence, fungal AMR/MDR, zoonosis and improvement in fungal detection methods (Firacative, 2020). The issue is further proliferated by the increasing number of emerging fungal pathogens including MDR *Candida auris*, *Fusarium* spp. and *Mucorales* (Yousfi et al., 2019). Additionally, rare and emerging moulds including *Lomentospora* spp. and *Scedosporium* species have innate AMR and represent a significant challenge in detection and diagnostics (Hoenigl et al, n.d.). Zoonosis is highly prevalent in fungal species (Table 2) with many species transmitting from food producing and companion animals (Meade et al., 2020b; Meade et al., 2019). The most common species associated with invasive infection, morbidity and mortality include *C. albicans*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Pneumocystis jirovecii* and *Mucoromycetes* (Firacative, 2020). Invasive mycosis is a significant challenge in clinical settings due to the vast array of fungal pathogens, limited number of antifungal drug-options, drug biocompatibility and absorption issues in the host.

When the terms funguria or fungal urinary tract infection are used, most physicians are referring to candiduria and urinary tract infections due to *Candida* species (Kauffman, 2014). Other fungi, including yeasts and moulds can involve the kidney during the course of disseminated infection, but rarely cause symptoms referable to the urinary tract. *Candida* species appear to be unique in their ability to both colonize and cause invasive disease in the urinary tract. Candiduria is commonly seen in hospitalized patients and most of the patients are asymptomatic, but it may be due to cystitis, pyelonephritis, prostatitis, epididymo-orchitis or disseminated candidiasis (Odabasi and Mert, 2020). Major risk factors are diabetes mellitus, indwelling urinary catheters, use of broad-spectrum antibiotics, urinary obstruction, and admission to ICUs. *Candida* urinary tract infections can be caused by hematogenous spread following candidemia, or retrograde route via the urethra. *Candida auris*, which was first isolated in 2009, has now become a global health threat with mortality rates of ca. 72 % (Hillock et al., 2022). While *C. albicans* is the leading cause of BSIs, diagnostics increasingly report *C. glabrata* as the cause of invasive fungemia in older patients (Kauffman and Yoshikawa, 2001). Importantly, *C. glabrata* possess innate resistance to fluconazole requiring treatment with echinocandin as drug therapy.

Cryptococcus neoformans and *C. gattii* are the predominant species associated with cryptococcosis where inhalation of the fungal spores leads to pneumonia with dissemination to the central nervous system (CNS) causing meningitis. In immunocompetent persons, the disease is often self-limiting due to the action of innate (neutrophils) and adaptive immunity, like TB; however, persistent infection with chronic systems can occur (Zafar et al., 2019).

Cryptococcus has a 20 % mortality rate in immunocompromised HIV patients (Pasquier et al., 2018) increasing to 100 % if left untreated (Iyer et al., 2021). Furthermore, *Cryptococcus* species are innately resistant to the echinocandins, have acquired resistance to azoles; therefore, treatment is limited to the nephrotoxic amphotericin B (AMPB) (Lee et al., 2020). Efforts to reduce AMP B toxicity and increase efficacy have led to the development of a combination therapy with flucytosine, a liposome bilayer-coated AMPB formulation, and an encochleated oral AMPB a lipid-containing crystal nanoparticle for delivery to the CNS in the treatment of meningitis (Jarvis

Table 2
Zoonotic pathogenic fungal species isolated from food producing and companion animals, where AMR profiles[a] and route of zoonosis are listed.

Isolate		Disease	AMR profile[a]	Route of zoonosis
Fungal species	*Candida albicans*	Canine cutaneous candidiasis	Resistant to FCZ, AMP B and CAS (Meade et al., 2019)	Close contact to the animal, animal bedding and/or excrement
	Candida krusei	Canine candiduria	Resistant to FCZ, AMP B and CAS (Meade et al., 2019)	
	Aspergillus niger	Canine otomycosis	Resistant to FCZ (Meade et al., 2021a, 2021b, 2021c)	
	Malassezia pachydermatis	Canine dermatitis	Resistant to FCZ, AMP B and CAS (Meade et al., 2021a, 2021b, 2021c)	
	Cryptococcus neoformans	Bovine mastitis	Resistant to FCZ, AMP B and CAS (Meade et al., 2020b)	Close contact to the animal, consumption of contaminated milk/dairy

Abbreviations: FCZ - Fluconazole, AMP B - Amphotericin B, CAS - Caspofungin.
[a] AMR profile established via selective agars, and standard disk diffusion and microdilution methods in accordance with EUCAST guidelines.

et al., 2019; Lu et al., 2019). Clinical trials are ongoing where initial studies show promising results (Iyer et al., 2021).

Aspergillus has 4 main manifestations of disease including allergic bronchopulmonary aspergillosis, chronic necrotising pneumonia, aspergilloma (mycetoma) and an invasive aspergillosis (Metodiev, 2012). Invasive aspergillosis commonly resultant from *A. fumigatus* infection has a mortality rate of ca. 70 % in immunocompromised patients (Firacative, 2020) where neutrophil dysfunction and neutropenia are risk factors for disease progression. Importantly, *Aspergillus* pneumonia can result in a chronic necrotizing infection with a mortality rate of 40 % (Latgé and Chamilos, 2019) increasing to 100 % in undiagnosed patients with dissemination to the CNS (Fosses Vuong and Waymack, 2022). Dissemination of aspergillosis resultant in endocarditis, endophthalmitis and abscesses on many organs, soft tissue and bone is also possible (Metodiev, 2012). There is increasing prevalence of azole resistance (fluconazole) in *A. fumigatus* isolates globally (Romero et al., 2019) with this class of drug being the primary treatment option for aspergillosis due to its oral administration, improved biocompatibility, and cost (Wiederhold, 2017). *Pneumocystis jirovecii* is an opportunistic pathogen and the causative agent of Pneumocystis Jirovecii Pneumonia (PJP) a potentially life-threatening pneumonia having a mortality rate of 50 % in immunocompromised persons (Truong and Ashurst, 2022) such as those suffering congenital immunodeficiency, AIDS, or receiving organ transplants (Lee et al., 2015). *P. jirovecii* can be carried asymptomatically by immunocompetent persons who act as reservoirs for transmission. Importantly, ergosterol is absent from the plasma membrane of *P. jirovecii* making many antifungal agents including AMPB and the azoles redundant in the treatment of PJP where anti-protozoan drugs where the mainstay of treatment (Helweg-Larsen et al., 2017).

Currently, standard treatment involves cotrimoxazole which contains sulfamethoxazole (SMX) and trimethoprim (TMP), SMX resistance, however, has become a concern in *P. jirovecii* (Lee et al., 2015). Both these antimicrobial's target the essential enzymes dihydrofolate reductase (DHFR) required for purine synthesis and dihydropteroate synthase. This makes them excellent antimicrobial drug targets, as disruption of thymine synthesis leads to cell death in many microorganisms (Ahmad et al., 1998). Mutations in the *DHFR* gene, however, confer TMP resistance in many microbial species including *P. jirovecii* (Leidner et al., 2021). In non-responsive PCP patients, treatment with a combination of caspofungin and clindamycin may offer some benefit (Li et al., 2016). Additionally, adverse drug reactions are common with cotrimoxazole treatment including fever, nausea, vomiting, neutropenia, thrombocytopenia, and epidermal necrolysis that can be fatal in some cases (Kaplan et al., 2009).

Mucoromycetes are a group of environmental moulds the Mucorales (*Rhizopus*, *Apophysomyces*, *Mucor*, and *Lichtheimia* species) associated with Mucormycosis (previously zygomycosis) a rare, severe, and often fatal fungal infection in humans having an 80 % mortality rate. The incidence of Mucormycosis is increasing however, as the population of immunocompromised patients increases (Skiada et al., 2020). Mucormycosis recently came to light in India in an infection outbreak in thousands of Covid-19 patients (Stone et al., 2021). Prolonged antibiotic and corticosteroid therapy are predisposing factors for Mucormycosis in Covid patients (SeyedAlinaghi et al., 2022) with diabetic patients and patients with hematological malignancies also at risk. A chronic progressive infection caused by *Mucor irregularis* has emerged in immunocompetent persons in China (Skiada et al., 2020). Mucormycosis targets numerous organs including the nasal cavity, paranasal sinuses, orbit fossa, CNS, pulmonary system, GIT, cutaneous, disseminated, and mediastinum (Nagy et al., 2021). The Mucorales have high levels of antifungal resistance with current treatments AMP B, posaconazole and isavuconazole only displaying suboptimal efficacy (Dannaoui, 2017). Drug therapy is therefore often in combination with surgical intervention.

2.2. Food security and fungal AMR

Agriculture is particularly susceptible to fungal infection and destruction leading to loss of production, national economic impacts, and impacts on human health (Gehlot and Singh, 2018). Contamination of the agricultural food chain with fungal species and/or their mycotoxins can result in food wastage, disease outbreak, morbidity, and economic burden. To mitigate the risk of fungal agricultural impacts azole-based fungicides (predominately imidazoles and triazoles) have been in use for decades (Jørgensen and Heick, 2021). Indeed, from a One Health perspective azoles offer effective management of many fungal disease in plants, animals and humans ensuring food security (Verweij et al., 2020). Environmental exposure to the azoles however, used as fungicides in agriculture, has promoted azole resistance in clinical fungal species including *Aspergillus* (Wiederhold, 2017). Such AMR has been observed in *A. fumigatus* which is harmless to plants but causes invasive fungal disease in humans, often fatal in immunocompromised patients (Verweij et al., 2020). Furthermore, disease management is an emerging issue in agriculture as azole resistance occurs in many plant fungal pathogens including *Zymoseptoria tritici*, *Pyrenophora teres* and *Ramularia collocygni* (Rehfus et al., 2019). Indeed, the abundant use of fungicidal agents in agriculture promotes AMR to all classes of antifungal agents including benzimidazoles, anilinopyrimidines, strobilurins, succinate dehydrogenase inhibitors and the sterol demethylation inhibitors (DMIs) (Fisher et al., 2022). While azole use in agriculture varies globally, patterns emerge between the use of azoles and rate of azole resistant strains. Holland for example, where azoles are used abundantly in tulip farming has one of the highest rates of azole resistance strains of *A. fumigatus* (van der Linden et al., 2013). As food security and zero hunger are goals of the UN SDGs there is a need to protect and enhance food production systems in a sustainable way. The introduction of mycopesticides to control insect species as part of sustainable agriculture is one such method. The use of fungal species non-pathogenic to humans may reduce the emergence of AMR species. Mycopesticides used as mycoherbicides (*Collectrichum gloesporioides*, *Phytophthora palmivoraa*), mycoinsecticides (*Beauveria bassiana*) and mycofungicides (*Trichoderma*) certainly offers some benefits towards sustainable agriculture practices (Gehlot and Singh, 2018). The use of entomopathogens has proven beneficial as alternatives to chemical pesticides due to their broad activity, environmental safety, lack of residual on food and safety for human contact. The entomopathogenic fungus *Beauveria bassiana* and bacteria *Bacillus thuringiensis* have displayed a range of possibilities as biopesticides for numerous crop pests (Wang et al., 2021). Entomopathogenic fungi are important regulators of insect populations and biotransformation of ecosystems aiding in biodiversity regulation (Niu et al., 2019). These fungi destroy insect species thereby lowering insect density on crops, preventing crop losses. They are common soil dwellers in natural habitats. Undesirable killings by entomopathogenic fungi are a risk however, where excess usage of these biopesticides may disrupt the biodiversity of soil or harm beneficial insects such as pollinators (Yaman, 2017). Laboratory studies demonstrated that some Beauveria and Metarhizium isolates cause significant mortality to honeybees, but this has not been verified in an environmental setting (Bava et al., 2022). It is essential to fully establish the impact of these fungi on biodiversity and essential species such as pollinators before increasing their widespread application. Additionally, such biopesticides may pose a risk to immunocompromised persons, require approximately 2 weeks to work and have expensive manufacture and storage requirements (Gehlot and Singh, 2018).

2.3. Biocidal AMR considerations

The extensive use of anthropogenic chemicals as biocides represents a great risk to environmental, animal, and human health (Massei et al., 2018). Depending on their application, biocides are categorised as disinfectants, preservatives, pesticides, and other biocidal products such as antifouling agents (Levinskaite, 2012). Such chemical pollution is a significant problem resulting in water and soil pollution, loss of soil fertility, loss of biodiversity, loss of ecosystems and bioaccumulation of fat-soluble chemicals and associated toxicity. Additionally, chemical pollution is believed to have resulted in 9 million premature deaths in 2015 and contribute to the growing trend in neuro-development issues in children including autism, attention deficit disorder, mental retardation, and cerebral palsy

Table 3
Common biocides used for the clinical control of pathogenic species, mode of action and resistance in clinically important species.

Biocide (classification)	Mode of action	Resistance mechanisms	Usage issues relating to AMR	Public health safety issues
Benzalkonium chloride (Quaternary ammonium compound -QAC)	Membrane active agents – membrane destruction (Heinrich et al., 2015) Fungistatic Membrane enzyme alterations Loss of osmo-regulation (Naughton et al., 2017)	Resistance mediated by species specific efflux pumps *Saccharomyces* spp. and fungal spp. *Aspergillus*, *Neurospora* and *Cryptococcus* spp. via efflux pumps (Meade et al., 2021c) Ineffective against planktonic *Candida* spp.	Effective dose must be increased to inactivate pathogens leading to residues in food and noncompliance with MRLs Influenced by bioburden Clinical species and foodborne	Promotes AMR, food pollution exceeding MRL, risk to public health safety
Triclosan (Phenolic compound)	Chlorhexidine is antimicrobial at high concentration, coagulation of cellular contents, nucleic acid and protein precipitation (Lachapelle et al., 2013)	Triclosan induces over expression of MDR efflux pumps (Cameron et al., 2019)	Increased contact time to achieve biocidal action, food pollution with triclosan or toxic triclosan by-products 2, 8-Dichlorodibenzo-p-dioxin and 2, 4-Dichlorophenol (Gómez-López and Bolton, 2016)	Bioaccumulation, foetal toxicity, endocrine toxicity (Chen et al., 2017) CNS toxicity in animals (Franssen et al., 2018) Environmental pollution - detected in aquatic ecosystems Detected in human urine and milk (Cameron et al., 2019)
Chlorhexidine (Biguanide)			No viricidal or sporicidal activity, limited pH range, resistance in *Candida auris* (Meade et al., 2021c)	Dermal irritation, environmental pollution, aquatic toxicity Weak allergen, good skin tolerance
Ethanol	Potent antimicrobial activity at 70–90 % (Sauerbrei, 2020) Decreases the rates of growth and fermentation and cell viability of yeast	Ethanol tolerance present in some species particularly yeast spp.	Exposure time varies ≤ 0.5 and ≥ 5 min. Exposure of up to 5 min - 80 %–90 % ethanol has virucidal/low-level activity - enveloped viruses	
Iodophor PVP-I, (Iodine)	Potent antimicrobial activity at Potent antimicrobial activity at 70-90 % (Sauerbrei, 2020)	A lack of chromosome- or plasmid-mediated resistance.	Dependant on the free iodine concentration. Maximum exposure times are 5 min for bacteria and 60 min for viruses.	Good skin tolerance (Lachapelle et al., 2013)

(Brack et al., 2022). The European Union (EU) implemented the EU Biocidal Products Regulation (BPR) No 528/2012 to regulate the market and use of biocidal products in order to mitigate environmental pollution. Certain unsafe biocides have been withdrawn from use and others are under investigation under this important regulation. Chemical risk assessment is key to establishing the safety profile of biocides where routes of exposure, hazard identification and safety levels are essential factors. The vast range of anthropogenic chemicals and their unpredictable combinations in the environment; however, makes such analysis extremely difficult. The rate of environmental pollution with persistent antimicrobial chemicals such as chlorine and quaternary ammonia compounds (QACs) is extensive, particularly in hotspot locations such as hospital effluent. QACs, which are broad spectrum antimicrobials, are toxic to aquatic species fish, algae and daphnids have been detected in surface and wastewater at 60 ppm (Meade et al., 2021a, 2021b, 2021c). The prevalence of biocidal resistance in AMR species bacterial and fungal (Table 3) is also an alarming trend where resistance to QACs has been shown to promote AMR in species including *E. coli* (Garvey, 2022). Studies report strains of *Pseudomonas aeruginosa*, which were 12 times more tolerant to certain QACs, were also 265 times more resistant to ciprofloxacin due to mutations in the *gyrA* gene (Chen et al., 2021). Indeed, many microbial species display biocidal resistance or tolerance to EPA approved disinfectants evident by increasing minimum inhibitory concentrations (MICs). Exposure to suboptimal or sublethal concentrations allows for the acquisition of AMR in bacterial and fungal species to many of the standard disinfectants including QACs, phenols and chlorine-based solutions (Levinskaite, 2012). The development of alternative green biocides for disinfection purposes may offer some benefits in reducing environmental pollution from disinfection activities (Garvey, 2022).

3. Efficacy of front-line infection preventive interventions

There are several front-line approaches used to inactivate fungal pathogens that vary in efficacy depending on the type of technology used, species of fungi treated, and environmental processing conditions. Emphasis is based on breaking the chain of infection using appropriate technologies and interventions that can be informed by predictive modelling (Rowan et al., 1999) and risk mitigation tools. This is an established HACCP approach that was also successfully used to prevent and control mycotoxins in grains (Matumba et al., 2021) and to addressing important supply chain disruption issues during the COVID-19 pandemic (Rowan and Laffey, 2020; Rowan and Laffey, 2021; Rowan and Moral, 2021). Prevention of fungal infections arising from reuse of medical devices is addressed by appropriate cleaning and reprocessing by the healthcare provider based on following manufacturer's instructions for use (MIFU), which is a highly regulated industry. However, if improperly cleaned and stored, reusable medical devices (such as contaminated endoscopes) can harbour fungal species (such as *Aspergillus* sp., *Candida* sp.) (Marchese et al., 2021) in build-up biofilm that can tolerate reprocessing including use of chemical or gaseous high-level chemical disinfection (Alfa, 2019; Alfa and Singh, 2020; Kwakman et al., 2022). Where appropriate, medical devices are subjected to physical terminal sterilization modalities (such as electron beam, gamma and x-ray irradiation), based on the complexity of design features and heat-sensitive material composition (Chen et al., 2019; McEvoy and Rowan, 2019). The healthcare Sterile Services Department follows MIFUs to understand and apply appropriate cleaning and reprocessing that includes conducting verification testing using artificial soiling procedures (Giles et al., 2018; Alfa, 2019).

Selection of appropriate medical device disinfection or sterilization approaches is informed by the Spaulding Classification system, which is based on the perceived risk to patient acquiring an infection due to use of a contaminated device (Fig. 1). Josephs-Spaulding and Singh, 2021 "Critical (items that contact sterile tissue, such as surgical instruments), semi-critical (items that contact mucous membrane, such as endoscopes), and non-critical (devices that contact only intact skin, such as stethoscopes), items require sterilization, high-level disinfection, and low-level disinfection, respectively" (Rutala, 2019). In terms of the hierarchy

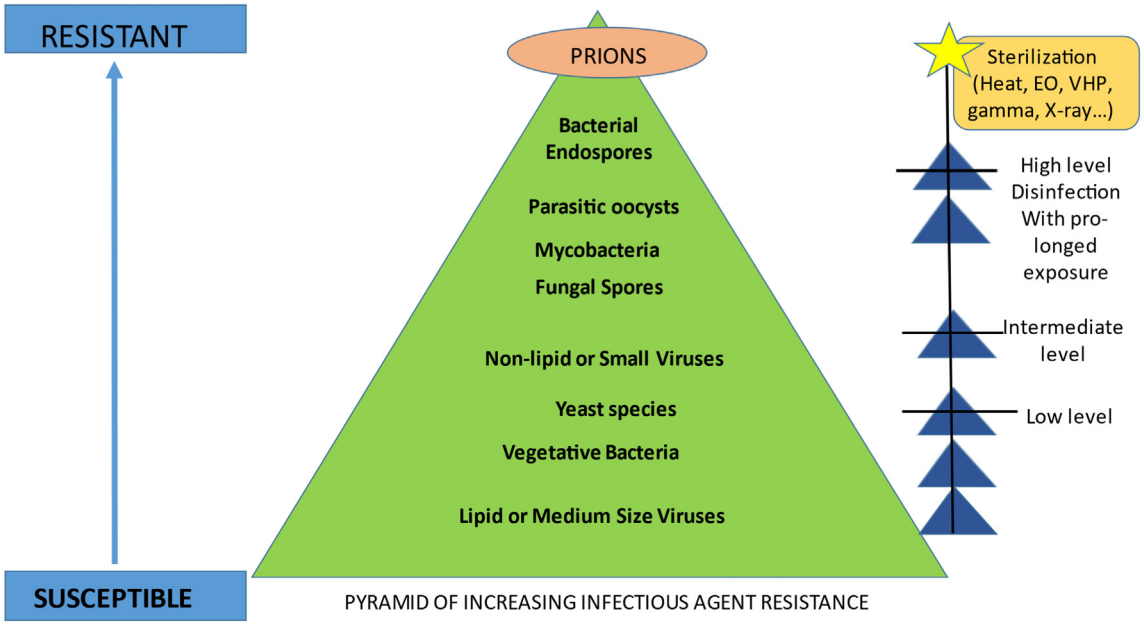


Fig. 1. Pyramid of increasing microbial and infectious agent resistance to disinfection and sterilization.

of susceptibility of different microbial species to the various applied lethal processing technologies, fungal spores are generally considered to be moderately resistant. Yeast cells are of similar resistance to vegetative bacterial cells when exposed to disinfection treatments (Fig. 1). While planktonic occurring yeast are typically killed by low-level disinfection, high-level disinfection or sterilization processes may be required to kill similar yeast species in build-up biofilm on improperly maintained medical devices, such as endoscopes. However, such yeast may survive device reprocessing if improper cleaning precedes high-level disinfection or sterilization. In situ healthcare, and terminal sterilization industry apply the principle of 12 D (Decimal Reduction Time) to ensure all medical devices are sterilized, which is a significantly over-kill approach based upon probability of achieving lethality where biological indicators (such as *Geobacillus stearothermophilus* or *Bacillus atrophaeus*) are treated with high levels of sterilant typically treated for these regulated modalities (Fig. 2). While there is a need to consider the sustainability of sterilant usage, there is also a significant lack of published work on the use of fungi in medical device reprocessing and sterilization.

Indwelling catheters are a high risk of colonization by systemic fungal infections (Kazemzadeh-Narbat et al., 2021). Giles et al. (2018) has

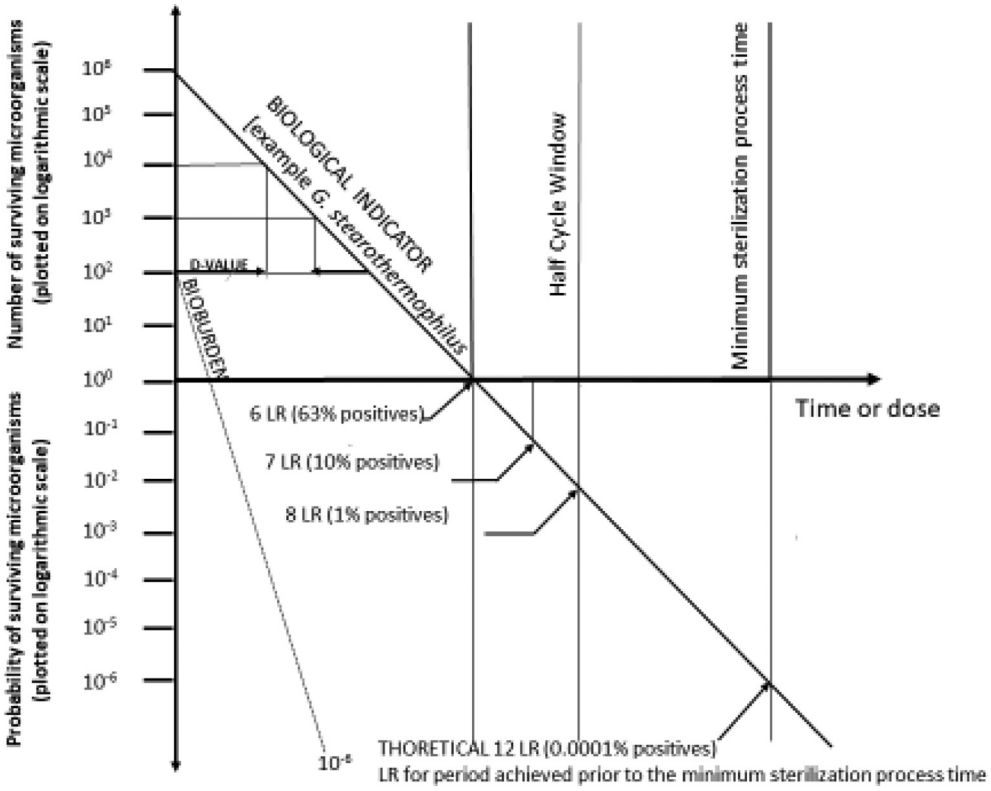


Fig. 2. 12-D microbial inactivation plot for establishing sterility assurance levels in treated devices (adopted from McEvoy and Rowan, 2019).

reported that there is increasing evidence fungal species, particularly *Candida*, can contribute to medical device infections that relate to colonization of devices such as indwelling catheters post insertion in patient. Fungal species can harbour in build-up biofilms that occur in improperly maintained reusable endoscopes where they are protected from high-level disinfection; moreover, these contaminated devices can cause infection particularly in compromised patients (Marchese et al., 2021; Kwakman et al., 2022). High-level disinfection is verified by reducing a pre-determined population of Mycobacterial species by 6 log orders; it does not destroy bacterial endospores Thus, there is a clear need for effective preventative measures, such as thin coatings that can be applied onto medical devices to stop the attachment, proliferation, and formation of device-associated biofilms (Masterson et al., 2021). However, fungi being eukaryotes, the challenge is greater than for bacterial infections because antifungal agents are often toxic towards eukaryotic host cells. While there is extensive literature on antibacterial coatings, a far lesser body of literature exists on surfaces or coatings that prevent attachment and biofilm formation on medical devices by fungal pathogens. Other emerging technologies used in healthcare and adjacent areas to prevent fungal diseases are as follows:

3.1. Light based disinfection technologies

Light based technologies for effectively destroying microbial pathogens including fungal spores have been low-pressure fixed UV (256 nm), broad-spectrum pulsed light (200 to 1100 nm) (Hayes et al., 2012a; Rowan, 2019; Garvey et al., 2010), and more recently, blue light (400 to 500 nm, or fixed at 405 nm) (Trzaska et al., 2017). These are non-thermal technologies that leave no unwanted chemical residuals and have been used for both contact surface and air disinfection (Garvey and Rowan, 2015). Reliable and repeatable destruction of fungal spores depends on duration of exposure, dose, fungal bioburden or population and presence of interfering material or milieu such as organic deposits or biofilm (Farrell et al., 2009; Garvey et al., 2015a). Therefore, prior cleaning of surfaces significantly enhances disinfection performance of light-based technologies, which equally applies for achieving appropriate sterility assurance levels for all modalities (McEvoy and Rowan, 2019). An understanding of inactivation kinetic modelling and performance of UV light sources is critical to achieve appropriate log-reductions in the intended target (Rowan and Moral, 2021; Rowan et al., 2015).

Low pressure, fixed wavelength (256 nm) UV light (LPUV) sources have been used for decades for disinfection of fungal spores on contact surfaces and relies upon the disruptive nature of UV to specifically target and irreversibly damage DNA (Fitzhenry et al., 2019). However, technical drawbacks to using fixed UV light sources include safety to operator due to UV exposure, adaptive molecular and cellular repair mechanisms in treated fungi, and the presence of spore pigmentation that absorbs UV light at the same or similar wavelength to 256 nm protecting the fungus (Anderson et al., 2000). Development of effective adaptive responses by fungi to UV irradiation is well understood given that UV is a constitute wavelength found in sunlight. Fixed-wavelength UV sources is mainly used for inactivation of waterborne pathogens including fungal spores (Wan et al., 2020). There is a gap in knowledge as to whether fungi exhibiting resistance to front-line antifungal drugs are more resistant; however, this is unlikely given LPUV focuses on DNA.

Pulsed UV light (PL) have been reported to effectively destroy a broad range of fungal pathogens, but this has been limited to contact surface disinfection due to safety exposure risk to operators. PL has been approved by the FDA in the production, processing and handling of foods since 1996 up to cumulative UV dose or fluence of 12 J cm^{-2} where emission spectra is to be kept between 200 and 1100 nm and pulse duration at ≤ 2 ms (Food and Drug, 1994). It is used for commercial scale food packaging. The technological principle of pulsed light disinfection is based upon the accumulation of high discharge voltage in a capacitor, where the stored energy is delivered in ultra-short pulses through a light source filled with xenon gas (Hayes et al., 2012b). This xenon-light source emits a broad-spectrum light flash typically in the range of ca. 200–1100 nm, with approximately 25 % in the UV range (Bradley et al., 2012). It is considered that PL disinfection efficiency is higher compared with continuous-wave low-pressure UV irradiation (CW-UV) due to its high peak power along with the ability to deliver its stored energy over short durations, typically 1 to 10 pulses per second (Rowan, 2019). The main parameters governing effective PL operational for disinfection are the fluence [J cm^{-2}] over exposure time [s], number of pulsed applied [n], pulsed width [τ], frequency [Hz], and the peak power [W] (Rowan, 2019; Hayes et al., 2013; Garvey et al., 2015b). Future sustainability surrounding the development of PL treatment is likely to entail use of different light sources such as LEDs (Kim et al., 2017) along with using different configuration in treatment chambers design that deliver pulsed light at multiple angles to overcome shaded areas (Chen et al., 2017). Murray et al. (2018) suggested that additional advantages of using LEDs are the potential to use a range of different wavelengths such as UV-C thereby providing a possible synergistic antimicrobial action (Murray et al., 2018). This approach may be particularly applicable for inactivating complex pathogens, such as fungi or parasites, where other wavelengths in the pulsed spectrum may also contribute by destroying important cellular macromolecules and structures (Garvey et al., 2013).

Farrell et al. (2011) reported on the relationship between pulsed UV light (PL) irradiation and the simultaneous occurrence of molecular and cellular damage in clinical strains of *Candida albicans* (Farrell et al., 2011). Microbial protein leakage and propidium iodide (PI) uptake assays demonstrated significant increases in cell membrane permeability in PL-treated yeast that depended on the amount of UV pulses applied. This finding correlated well with the measurement of increased levels of lipid hydroperoxidation in the cell membrane of PL-treated yeast. PL-treated yeast cells also displayed a specific pattern of intracellular reactive oxygen species (ROS) generation, where ROS were initially localised in the mitochondria after low levels of pulsing (UV dose 0.82 μJ/cm^2) before more wide-spread cytosolic ROS production occurred with enhanced pulsing. Intracellular ROS levels were measured using the specific mitochondrial peroxide stain dihydrorhodamine 123 and the cytosolic oxidation stain dichloroflurescin diacetate. Use of the dihydroethidium stain also revealed increased levels of intracellular superoxide as a consequence of augmented pulsing. The ROS bursts observed during the initial phases of PL treatment was consistent with the occurrence of apoptotic cells as confirmed by detection of specific apoptotic markers, abnormal chromatin condensation and externalisation of cell membrane lipid phosphatidylserine. Increased amount of PL-irradiation (ca. UV does 1.24–1.65 μJ/cm^2) also resulted in the occurrence of late apoptotic and necrotic yeast phenotypes, which coincided with the transition from mitochondrial to cytosolic localisation of ROS and with irreversible cell membrane leakage. Use of the comet assay also revealed significant nuclear damage in similarly treated PL samples. Although some level of cellular repair was observed during sub-lethal exposure to PL-treatments (≤ 20 pulses or UV dose 0.55 μJ/cm^2), this was absent in similar samples exposed to increased amounts of pulsing. Therefore, PL-irradiation inactivates *C. albicans* through a multi-targeted process with no evidence of microbial ability to support cell growth after ≤ 20 pulses. Interesting, the identification of the onset of apoptosis in treated yeast coincided with irreversible cell death, which may be potentially used as a rapid diagnostic test for confirming their destruction, thus alleviating reliance on culture-based enumeration techniques that requires several days to confirm effectiveness (Farrell et al., 2011; Farrell et al., 2009).

Blue light is an emerging technology for destruction of fungal pathogens using spectral wavelengths that are safe for human exposure (Moorhead et al., 2016). Maclean et al. (2009) first reported on the inactivation of bacterial pathogens following exposure to light from a 405 nm light emitting diode, where Gram positive bacteria were more susceptible than similarly treated Gram negative bacteria (Maclean et al., 2009). Trzaska et al. (2017) exposed six-common trauma-associated fungal pathogens (*Rhizopus microsporus*, *Mucor cirinelloides*, *Scedosporium apiosspermum*, *Scedosporium prolificans*, *Fusarium oxysporum*, *Fusarium solari*) along with *Candida albicans* to blue light treatments at 405 nm (Trzaska et al., 2017). While blue light was shown to be highly effective against *Scedosporium*

and *Fusarium* spp., time lapse imaging revealed that *Rhizopus microsporus*, *Mucor circinelloides* and *C. albicans* eventually recovered full growth capacity. The authors noted that once established in the host, IFIs are very difficult to treat and are associated with high levels of morbidity and mortality where they recommended appropriate solutions to decontaminate hospital air, decolonize hospital surfaces to reduce opportunities for wound infection. Blue light appears to be effective against a range of pathogens, including certain fungi, and does not require the need for exogenous photosensitizer that are used in combinational photodynamic therapy (PTD). Zhang and co-workers (2014) demonstrated efficacy of blue light against antibiotic-resistant *Acinetobacter baumannii* in a mouse burn model of infection (Zhang et al., 2014). These authors also demonstrated that bacteria are more susceptible to blue light than keratinocytes, suggesting potential applications in topical treatments. The proposed mechanisms underpinning mechanistic action of blue light is photoexcitation of endogenous porphyrins, generating the production of ROS and cell death; however, this has yet to be elucidated (Moorhead et al., 2016). Moorhead et al. (2016) demonstrated efficacy of blue light for destroying *Trichophyton* and *Aspergillus conidia* by violet-blue light exposure (3380–480 nm) (Moorhead et al., 2016). Blue light technology that underpins High-Intensity Narrow-Spectrum light Environmental Decontamination System (HINS-light EDS) have now been deployed in many hospitals worldwide for the safe disinfection of air (Bache et al., 2012; MacLean et al., 2013). Recently, this technology was proven to completely inactivate the blood borne parasite *Trypanosoma cruzi* (that causes Chagas disease) in stored human platelet concentrates and plasma, which highlights potential for preventing adjacent fungal infections (Jankowska et al., 2020).

3.2. Other established and emerging interventions for preventing fungal infections

Flash heat pasteurization has been successfully used to treat microbial pathogens including fungi for the dairy industry for decades (Garnier et al., 2017), which is particularly relevant for species associated with causing mastitis (Kalińska et al., 2017). However, these authors also reported that prevention and control of the occurrence of fungi is a major concern for industrials and scientists that are looking for efficient eco-solutions. Several traditional methods, also called traditional hurdle technologies, are implemented and combined to prevent and fungal control include good manufacturing and hygiene practices, air filtration, and decontamination systems, while linked control methods encompassing inactivation treatments, and temperature control. While the use of inappropriate and excessive use of antibiotics in dairy cows has contributed to increased resistance of mastitis pathogens (Jamali et al., 2014), the contribution of fungi to disease burden is significantly underestimated and underappreciated as they are frequently overlooked. Other physical emerging technologies considered for reducing fungal pathogens in the environment includes the use of pulsed-plasma gas-discharge (PPGD) treatments, such as for industrial effluents (Rowan et al., 2007), and pulsed electric fields (PEF) (MacGregor et al., 2000; Beveridge et al., 2002). However, Hayes et al. (2013) reported that PPGD treatment can be unsafe for treating industrial effluents as this technology can produce considerable significant cytotoxic properties (as determined by MTT and neutral red assays), genotoxic properties (as determined by comet and Ames assays), and ecotoxic properties (as determined by Microtox™, Thamnotox™ and Daphnotox™ assays), which was attributed to corrosion of the electrodes over time (Hayes et al., 2013). However, Kang et al. (2015) reported on the effective inactivation of fungal spores in water and on seeds by using ozone and arc discharge plasma (Kang et al., 2015). Whereas Dehghani et al. (2007) previously reported on an ultrasound reactor technology to reduce fungi in sewage (Dehghani et al., 2007). The challenges with novel and new emerging technologies are gaining consensus internationally on agreed methodology that will produce harmonized findings that will inform verification for validation of modalities by regulators. This will also impact upon investors for bringing new technologies, including new green-deal innovations to market (Rowan and Galanakis, 2020; Galanakis et al., 2021).

There is commensurate interest the development of antifungal coatings to prevent medical device infections, particularly for *Candida* species (Giles et al., 2018). These authors report that fungal species can form biofilms by themselves or by participating in polymicrobial biofilms with bacteria. Thus, there is a clear need for effective preventative measures, such as thin coatings that can be applied onto medical devices to stop the attachment, proliferation, and formation of device-associated biofilms. However, as fungi are eukaryotes, there is a greater challenge than treating other microbial pathogens as antifungal agents are often toxic towards eukaryotic host cells. These authors noted that while there is extensive literature on antibacterial coatings, a far lesser body of literature exists on surfaces or coatings that prevent attachment and biofilm formation on medical devices by fungal pathogens. A greater appreciation of the molecular understanding of fungal recognition of, and attachment to, suitable surfaces, and of ensuing metabolic changes, is essential for designing rational approaches towards effective antifungal coatings, rather than empirical trial of coatings. With increasing complexity in the design of medical devices comes a commensurate challenge in the effective decontamination and sterilization, including devices for reuse (McEvoy and Rowan, 2019). There is a pressing need to establish appropriate real-time diagnostic technologies that will confirm efficacy of terminal sterilization processes for next-generation medical devices that balances microbial inactivation with maintaining effective material and design functionality of these devices post treatments (McEvoy et al., 2021).

Interest in the development of immunotherapies for addressing complex microbial infections has increased, particularly over the past decade, where invasive infections occur mainly as a result of altered immune status (Armstrong-James et al., 2017; Murphy et al., 2020; Murphy et al., 2021; Casalini et al., 2021). The incidence of IFIs has increased mainly due to the widespread use of immunosuppressive drugs, invasive medical interventions, HIV (Armstrong-James et al., 2017) and COVID-19 (Casalini et al., 2021; Roudbary et al., 2021). Thus, fungal diseases cause life-threatening infections in the context of primary and acquired immunodeficiencies all over the world. Invasive fungal diseases are associated with >50 % mortality that stems mainly from inadequate diagnosis and from clinical shortcomings of existing antifungal drugs (Armstrong-James et al., 2017; Vallabhaneni et al., 2016). However, no clinical vaccine exists for the main genera of fungi causing invasive diseases (*Aspergillus*, *Candida*, *Cryptococcus* and *Pneumocystis*) (Armstrong-James et al., 2017). The close relationship between infection susceptibility and immunocompromised status, combined with poor outcomes and increasing resistance to conventional antifungal chemotherapy, has intensified interest in immunotherapies. The rapid progress in clinical immunotherapy research is creating unprecedented opportunities to exploit existing approaches for treatment of fungal disease—from recombinant cytokines to vaccines, monoclonal antibodies, and engineered T cells (Armstrong-James et al., 2017). However, these authors advocated that the biggest challenge in the next decade will be to test the use of immunotherapy for fungal diseases in carefully designed clinical trials (Armstrong-James et al., 2017). The central role of phagocytic cells in protective innate host response and in the development of adaptive immunity is increasing in focus, where phagocytes are therapeutic targets as their activities can be influenced by soluble immunomodulatory mediators (Wüthrich et al., 2012). The incidence of mycoses is rising because immunomodulatory drugs are increasingly used to treat autoimmune diseases and cancer. New classes of antifungal drugs have only been partly successful in improving the prognosis for patients with fungal infection. Armstrong-James et al. (2017) advocated that adjunctive host-directed therapy is therefore believed to be the only option to further improve patient outcomes (Armstrong-James et al., 2017). Recent advances in the understanding of complex interactions between fungi and host have led to the design and exploration of novel therapeutic strategies in cytokine therapy, vaccines, and cellular immunotherapy, each of which might become viable adjuncts to existing antifungal regimens. However, outcomes of several studies support an association between genetic polymorphisms and increased risk of fungal infections such as patients who have received transplants (Maskarinec et al., 2016), where Armstrong-

James et al. (2017) suggested stratifying patient risk on the basis of immunogenetics (Armstrong-James et al., 2017). In doing so, intensive diagnostic screening alone or combined with prophylactic antifungal therapy can inform targeted immunotherapy to address this issue. Immunotherapy can potentially circumvent increasing prevalence of increased resistance to front line antifungal drugs in infected animals and humans.

3.3. Occurrence, fate and ecological risk of anti-fungal drugs and personal care products

Currently, 400,000 tons of fungicides are applied to food crops globally, which represents 17.5 % of pesticide applications (Gikas et al., 2022). Researchers have reported that popular azole fungicides may reach the receiving environment by direct or indirect discharge of wastewaters; thus, posing significant potential risks to organisms in aquatic ecosystems (Chen and Ying, 2015; Bhagat et al., 2021). Azole fungicides are widely detected in surface water and in sediment of the aquatic environment arising from incomplete destruction or removal in wastewater treatment plants. Assress et al. (2021) reported that azole antifungals may enter the environment through the discharge of domestic, industrial and hospital wastewaters, agricultural runoffs and as leachates in waste-disposal sites. These authors noted that the presence of the azole antifungals poses potential toxicity risks to non-target organisms and plays a critical role in the evolution and/or selection of azole resistant fungal strains in the environment. These fungal drugs were reported to be resistant to microbial degradation but undergo photolysis during exposure to UV irradiation (Chen and Ying, 2015). However, photolysis of azole and effect of its derivatives need to be further studied. Due to variance in physicochemical properties and environmental persistence, these azole drugs could cause toxicity to aquatic organisms such as algae (Nong et al., 2021) and fish (Bhagat et al., 2021). Azole fungicides were recently reported to be potent disrupting chemicals for fish that can significantly affected their reproductive system; moreover, steroid hormone disruption may be novel toxicity in fish (Huang et al., 2022). Toxicities such as inhibition of algal growth, endocrine disruption in fish, CYP450-effected steroidogenesis, modulating sex differentiation in frogs, and reduction of larval body mass and growth rate have been related to azole antifungals (Assress et al., 2021). In addition, the isolation of azole resistant fungi such as *Aspergillus fumigatus* in both the environment and clinic retaining similar mode of molecular drug resistance mechanism has drawn the attention of many researchers (Assress et al., 2021). Therefore, the investigation of the occurrence and distribution of azole antifungals as well as azole resistant environmental isolates of fungi is merited. New solutions are pressing in order to effective remove azole fungicides potentially through alternative treatment technologies such as pulsed plasma gas discharge technologies along with better understanding environmental fate and toxic pathways in aquatic organisms. Multigenerational studies with environmentally relevant concentrations of antifungal drugs such as azole need to be considered (Bhagat et al., 2021). Indeed, based on current knowledge and studies reporting adverse biological effects of antifungal azole on fish, considerable attention is required for better management and effective ecological risk assessment of these emerging contaminants.

3.4. Established and emerging control strategies

Use of antifungal drugs remain the main control intervention for the treatment of disease where this market commands a demand of over $4 billion per year. Based on review of the total market demand, the main antifungal drugs used are azoles that represent over half of this market along with echinocandins and polyenes. However, despite the huge demand for appropriate and effective antifungal drugs, only one anti-fungal drug has been approved for therapeutic use over the past decade (Alanio and Dd, 2020). Approved antimycotics inhibit 1,3-β-d-glucan synthase, lanosterol 14-α-demethylase, protein, and deoxyribonucleic acid biosynthesis, or sequestrate ergosterol (Houšť et al., 2020). These authors reviewed licensed antifungal drugs and summarised their mechanisms of action, pharmacological profiles and susceptibility to specific fungi. The most severe side effects of antifungal drugs are hepatotoxicity, nephrotoxicity, and myelotoxicity. Whereas triazoles exhibit the most significant drug–drug interactions, echinocandins exhibit almost none. The antifungal resistance may be developed across most pathogens and includes drug target overexpression, efflux pump activation, and amino acid substitution (Houšť et al., 2020). These authors advocated that siderophores in the Trojan horse approach, or the application of siderophore biosynthesis enzyme inhibitors represent, the most promising emerging antifungal therapies. Sousa et al. (2020) reported that the high incidence of fungal infections has become a major public health issue (Sousa et al., 2020). These authors noted that despite the availability of drugs on the market to treat these diseases, their efficiency is questionable, and their side effects cannot be neglected. Consequently, it is important to synthetize new and innovative carriers for these antifungal drugs that addresses the emerging fungal infections along with the issue of increased in drug-resistant strains. Sousa et al. (2020) reported that new nano-based drug delivery systems and cellular targets/compounds with antifungal potential are under development (Sousa et al., 2020). However, there are pressing challenges in the translation of these natural compounds into the clinical pipeline.

Fungal urinary tract infections (funguria) are rare in community medicine, but common in hospitals, where 10 to 30 % of urine cultures isolate *Candida* species. Clinical features vary from asymptomatic urinary tract colonization (the most common situation) to cystitis, pyelonephritis, or even severe sepsis with fungemia (Etienne and Caron, 2007). The pathologic nature of funguria is closely relates to host factors, and management depends mainly on the patient's underlying health status. Microbiological diagnosis of funguria is usually based on a fungal concentration of $>10^3/mm^3$ in urine. No cut-off point has been defined for leukocyte concentration in urine. *Candida albicans* is the most commonly isolated species but previous antifungal treatment and previous hospitalization affect both species and susceptibility to antifungal agents. Treatment is recommended only when funguria is symptomatic or in cases of fungal colonization when host factors increase the risk of fungemia. The antifungal agents used for funguria are mainly fluconazole and amphotericin B deoxycholate because other drugs have extremely low concentrations in urine. Primary and secondary preventions are essential. The reduction of risk factors requires removing urinary catheters, limiting antibiotic treatment, and optimizing diabetes mellitus treatment.

The presence of *Candida* species in urine in asymptomatic patients does not warrant antifungal therapy except neutropenic patients, very low-birthweight infants and patients undergoing urologic procedures. Fluconazole is the treatment of choice for symptomatic infections, it achieves high urinary levels. The other azole antifungals and echinocandins do not reach sufficient urine levels. Amphotericin B deoxycholate is the alternative antifungal agent if fluconazole cannot be used because of resistance, allergy or failure.

Fungal pathogens, and zoonotic cross over species, however, remain an important public health consideration within the One Health approach. A One Health approach is vital to address the impact of AMR by way of identifying appropriate alternative solutions and to raise an awareness of the antimicrobial resistance crisis (Masterson et al., 2021). Fungal infections of sporotrichosis, histoplasmosis and chromoblastomycosis and MDR dermatophytosis remain important as zoonotic fungal pathogens. Furthermore, the impact of global warming will undoubtedly promote a rise in fungal infectious disease globally negatively impacting public health and food security.

Emerging opportunities now potentially exist for the development of specific phage therapies to address fungal pathogens (Górski et al., 2019). These authors reported that while the true value of phage therapy (PT) in human bacterial infections still awaits formal confirmation by clinical trials, new data have been accumulating indicating that in the future phage therapy may be applied in the treatment of non-bacterial infections, such as against *Aspergillus* that affect CF patients. Phage therapy will be potentially accelerated by hurdling uncertainty surrounding legal classification of phase therapy from a regulatory approval perspective in the Europe. Species-specific phages can be developed and applied for systemic and for

topical administration. While phages have been developed to treat a variety of significant bacterial infections in animals including poultry, cattle, pigs, sheep, swine, horses and fish (Alomari et al., 2021; Garvey, 2020); the topic remains to be properly advanced as producers are not harmonized where selection of phages is complicated. Xu et al. (2022) have recently reported on the use of phage nanoparticles as a carrier for controlling fungal infections (Xu et al., 2022).

3.5. Detection of fungal species is important in proper diagnosis and treatment

Fungal infections are typically diagnosed late or by chance due to gap of appropriate highly sensitive and specific diagnostic assays (Wen et al., 2020). Moreover, the clinical manifestations of IFIs are frequently non-specific and easily masked by primary underlying diseases (Wen et al., 2020). Early diagnosis is difficult, often resulting in delayed diagnosis, misdiagnosis, and delayed treatment. It is notable that IFIs have a poor prognosis and are associated with high mortality (Ibáñez-Martínez et al., 2017) as attested by ca.1.4 million deaths globally per annum (Sanglard, 2016). Sun et al. (2015) reported that the total mortality rate with invasive fungal species is 13.4 % (Sun et al., 2015), reported that the mortality rates associated with invasive candidiasis (IC) and invasive aspergillosis are 36 % to 63 % and 70 % respectively (Barnes, 2008), which supports the need for improvements in detection methods. Laboratory detection of invasive fungal species mainly involves traditional detection methods including direct microscopy, culture, and histopathology (Clancy and Nguyen, 2013). It is notable that traditional methods have a low positive detection rate along with poor sensitivity that does not enable real time clinical diagnosis (Garey et al., 2006). Serological analysis typically includes use of 1,3-β-D-glucan test (G test), galactomannan test (GM test), and latex agglutination test. While these approaches potentially enable early diagnosis of fungal infections, false-positive results do occur (Taccone et al., 2015) and they are not accurately detecting fungal species. Molecular biology technologies based on PCR have been widely used to detect (Powers-Fletcher and Hanson, 2016). Wen et al. (2020) recently reports on the use of fluorescence PCR melting curve analysis (MCA) as an emerging detection method for identifying fungal species without sequencing (Wen et al., 2020). These authors report that MCA has a high sensitivity, throughput, speed, and accuracy that is cost effective and is applicable for detecting fungal infections. Lengerova and co-workers (2014) noted that this method is based on the principle that different double-stranded DNA molecules have different Tm values, and changes in the shape of the melting curve can be monitored using fluorescent dyes or probes to detect and identify various fungi rapidly and accurately (Lengerova et al., 2014). Researchers have demonstrated efficacy for using combined probe-high resolution melting analysis for detecting *Candida*, *Cryptococcus*, *Aspergillus Mucor*, *Rhizopus*, and endemic diseased-related fungi (Wen et al., 2020; Alonso et al., 2012).

3.6. Mycosis and co-morbidity of COVID-19

Casalini et al. (2021) commensurately reported that IFIs can complicate the clinical course of COVID-19 and are associated with a significant increase in mortality, especially in critically ill patients admitted to an ICU (Casalini et al., 2021). The authors reviewed 4099 cases of IFIs in 58,784 COVID-19 patients involved in 168 studies. COVID-19-associated invasive pulmonary aspergillosis (CAPA) is a diagnostic challenge because its non-specific clinical/imaging features and the fact that the proposed clinically diagnostic algorithms do not really apply to COVID-19 patients. Forty-seven observational studies and 41 case reports have described a total of 478 CAPA cases that were mainly diagnosed based on cultured respiratory specimens and/or biomarkers/molecular biology, usually without histopathological confirmation. Candidemia is a widely described secondary infection in critically ill patients undergoing prolonged hospitalization, and the case reports and observational studies of 401 cases indicate high crude mortality rates of 56.1 % and 74.8 %, respectively. COVID-19 patients are often characterised by the presence of known risk factors for candidemia such as in-dwelling vascular catheters, mechanical ventilation, and broad-spectrum antibiotics. Studies also describe 3185 cases of mucormycosis (including 1549 cases of rhino-orbital mucormycosis (48.6 %)), for which the main risk factor is a history of poorly controlled diabetes mellitus (>76 %). Its diagnosis involves a histopathological examination of tissue biopsies, and its treatment requires anti-fungal therapy combined with aggressive surgical resection/debridement, but crude mortality rates are again high: 50.8 % in case reports and 16 % in observational studies. Roudbary et al. (2021) also patients with severe COVID-19, such as individuals in ICU, are exceptionally susceptible to bacterial and fungal infections (Roudbary et al., 2021). The most prevalent fungal infections are aspergillosis and candidemia. Other fungal species (for instance, *Histoplasma* spp., *Rhizopus* spp., *Mucor* spp., *Cryptococcus* spp.) have recently been increasingly linked to opportunistic fungal diseases in COVID-19 patients. These fungal co-infections are described with rising incidence, severe illness, and death that is associated with host immune response.

Roudbary and co-workers (2021) advocated creating greater awareness of the high risks of the occurrence of fungal co-infections, particularly as to downgrading any arrear in diagnosis and treatment to support the prevention of severe illness and death directly related to these infections (Roudbary et al., 2021). Since the onset of the COVID-19 pandemic, there are still few data on the prevalence of co-infections in patients with COVID-19 pneumonia. Yet, some studies already mention the problem of co-infections and drug resistance, which is the case of *Candida* spp. and COVID-19-associated superinfection mycosis, and its high potential for antifungal resistance (Roudbary et al., 2021; Heard et al., 2020). Indeed, around 21 % of patients who were under treatment with antifungals (voriconazole, isavuconazole, and caspofungin) showed no survival benefit (Rezasoltani et al., 2020). Zhou et al. reported that almost 50 % of mortalities accrued in patients had secondary bacterial and fungal infections (Zhou et al., 2020). This is the reason why antibiotics have been prescribed for hospitalized patients, for example, as a prophylactic measure against secondary infections, regardless of the susceptibility of the microorganism, promoting the emergence of multiple drug-resistant microbial species (Rawson et al., 2021). Roudbary et al. (2021) noted that COVID-19 was highly associated with pulmonary aspergillosis and candidemia (invasive candidiasis), which were increasingly recognised as the main fungal diseases (Roudbary et al., 2021); however, a shift has been occurring towards other fungal infections such as infections related to *Mucor* and *Rhizopus* genera, *Cryptococcus* spp. and other less common species. Generally, these authors noted that COVID-19 patients in ICU seem more susceptible to fungal infections, when compared with patients without ICU admission, due to their immunosuppression status (the same case of HIV patients). Several predisposing factors including diabetes, previous respiratory pathology, nosocomial infection sources and immunosuppressive therapy is associated with co-infections (Roudbary et al., 2021).

4. Additional considerations for developing and labelling eco-friendly biocides and other physical disease mitigation interventions

With such extensive application of fungicides globally to ensure food security and food safety, there must be awareness of the extent of environmental impact of these compounds. Environmental concerns and the need for associated protection have been influencing our approach to exploring new eco-friendly solutions for addressing disease mitigation (Silva et al., 2019; Rowan et al., 2021; Nallal et al., 2022). Both the hydrosphere and biosphere have been experiencing the negative impact of many pollutants, particularly when released to the marine environment (Tiedeken et al., 2017; Silva et al., 2019). Development of new eco-friendly biocides for addressing fungal pathogens need to comply with EU Biocidal Products Regulation (BPR) standards. There is a commensurate need to apply the full battery of ecotoxicology tests on these products that includes appropriate use of in vitro cell culture (Garvey et al., 2015b; Rowan, 2019). Some research has reported on partial use of ecotox batteries for important new innovation and processes (O'Neill et al., 2019), which requires further expansion. Rowan et al. (2021) highlighted key parameters associated with chemical biocides that must be considered for both efficacy and low

environmental impact that included type of biocide, concentration, pH There is growing interest in alternative or complimentary physical treatments for eliminating pathogens in clinical, industrial and municipal effluent; however, care must also be taken to ensure that these modalities do not generate additional toxic residues that may form as part of the biocidal process, such as through electrode erosion when using pulsed plasma gas discharge (Hayes et al., 2013). Nallal et al. (2022) described eco-friendly synthesis of multi-shaped crystalline silver nanoparticles using Hill garlic-Malai Poondu extract along with their potential effective applications against *C. glabrata*, *C. tropicalis*, *C parapsilosis*, *C. krusei* and *C. albincas*. The latter research is representative of increasing activities to the synthesis of metal nanoparticles using greener methodologies. For example, Narayanan and Park (2014) reported on the synthesis of silver nanopartilces using turnip leaf extract and its effectiveness against wood-degrading fungal pathogens. There are increasing opportunities to align development of eco-friendly biocides with sustainability tools such as life cycle assessment, material flow analysis, principle component analysis and so forth in order to provide companies with full risk assessments from a development and business-model perspective, which will inform new Green Deal era (Rowan and Pogue, 2021; Ruiz-Salmon et al., 2021; Laso et al., 2022). There is also a commensurate need to comprehensively consider eco-labelling of these products which are potential vast (Kahhonen and Nordstron, 2008). There is strong potential for combining new eco-friendly innovative biocides with biosurfactants that includes targeting complex biofilms and to prevent biocorrosion (Plaza and Achal, 2020).

5. Other pressing topics associated with ensuring effective prevention and control of fungal infections

Due to the enormity of the challenge at hand, there is a pressing need to develop appropriate digital technologies that will enable end-to-end monitoring of the effectiveness of new prevention and control technologies, and combinations thereof (Rowan et al., 2022). This will enable real-time monitoring of effectiveness that will also inform appropriate design-thinking that will positively transform interdisciplinarity efforts across manufacturers, producers, end-users and regulators for new innovation uptake and regulatory approval. For example, there are opportunities to apply artificial intelligence and to develop robotics in the area of device cleaning and reprocessing that will help remove potential human operator error and will increase the efficiency of reprocessing. Also, the introduction of immersive technologies for upskilling and reskilling workforce that will provide bespoke training to stakeholders including original equipment manufacturers, healthcare staff (such as Sterile Services Department), and external contract service providers (such as terminal sterilization). Candidate digital technologies are likely to emerge for adjacent additive manufacturing, digital twin, agriculture 4.0 and industry 5.0 human centric initiatives that includes digital twin (Rowan, 2020). Digital technologies that will impact positively include internet of things (IoT), cloud-edge computing, artificial intelligence including machine learning, robotics and use of blockchain that will address security of data, risk mitigation and disruptive business model development (Rowan et al., 2022). The generation, modelling and analysis of data governing efficacy of fungal disinfection will improve sustainability, such as by enabling greater reuse of important medical devices along with less use of single-use disposables, which will impart positively on clinical waste management and cost-effectiveness. MacNeill et al. (2020) noted that 'take-make-waste' is inherently unsustainable model of production and consumption as this contributes to global ecological destruction by depleting natural resources and generates excessive solid waste, global greenhouse gases, and other harmful environmental emissions. There is also a pressing need to use machine learning to help apply solutions for real-time decision-making to unlock plethora of complex factors influencing novel non-thermal processing of foods that includes antifungal applications (Gómez-López et al., 2022). Commensurately, there is a need to create a greater awareness in society about the prevalence and significance of fungal diseases including increased resistance to front-line interventions that will improve behaviour change and ultimately, decisions by policy makers (Suanda et al., 2013; Domegan, 2021). Effectively addressing fungal pathogens will contribute significantly to meeting several key Sustainable Development Goals of the United Nations (Rowan and Casey, 2021; O'Neill et al., 2022) including zero hunger, good health and well-being, quality education, industry, innovation and infrastructure, and responsible consumption and production.

6. Concluding remarks

There is increased evidence of adaption and resistance of pathogenic fungi to front-line anti-fungal drugs in animals and humans. IFIs can be particularly problematical in hosts that have a compromised immunity as evidenced by opportunistic IFIs in patients during HIV and COVID-19 pandemics. Greater information is required on appropriate selection and dose of antifungal drugs along with discovering solutions such as immunotherapies. Many front-line biocides are effective for addressing fungal spores; but, there is potential for cross-protection to antifungal drugs. There is a lack of information on efficacy of established disinfection technologies, particularly in the appropriate cleaning of contaminated medical devices that may contain biofilm harbouring infectious fungi. There is intensive research emerging on the development of alternative and complementary innovation that has anti-fungal applications, such as using blue light for air disinfection in healthcare including surgical theatres. Fungal spores present challenges for cleaning and aseptic processing for medical devices; however, the combinational use of terminal sterilization modalities will ensure appropriate sterility assurance levels are achieved. There is a pressing need to develop further appropriate real-time monitoring and diagnostic methods for fungal pathogens and to create a greater awareness as to contribution of fungal pathogens in disease causation, particularly co-infection in immunocompromised patients to improve outcomes. There is also a need to address risk mitigation and modelling to inform efficacy of appropriate intervention technologies that must consider all contributing factors to break the chain of infection including appropriate anti-fungal coatings on indwelling catheters. International consensus must be reached on standardised protocols for developing and reporting on appropriate intervention technologies that embraces emerging anti-fungal resistant strains, such as using a One Health platform.

Funding

The authors thank Interreg Atlantic Area Neptunus Project (EAPA_576/2018) and the Regional University Network - European Universities (RUN_EU) Project for funding supporting relating to this article.

CRediT authorship contribution statement

Conceptualization of this article was by MG and NR. Design, research, and writing of this article was conducted by EM, NR and MG. All authors approve the submission of this article.

Data availability

No data was used for the research described in the article.

Declaration of competing interest

The author declares no conflict of interest.

Acknowledgments

MG and EM would like to acknowledge the PEM centre and ATU Sligo.

References

Ahmad, S.I., Kirk, S.H., Eisenstark, A., 1998. Thymine metabolism and thymineless death in prokaryotes and eukaryotes. Annu. Rev. Microbiol. 52, 591–625.

Alanio, A., Dd, G.F.S.-P.P., 2020. Global Action Fund for Fungal Infections (GAFFI).

Alfa, M.J., 2019. Biofilms on instruments and environmental surfaces: do they interfere with instrument reprocessing and surface disinfection? Review of the literature. Am. J. Infect. Control. https://doi.org/10.1016/j.ajic.2019.02.027.

Alfa, M.J., Singh, H., 2020. Impact of wet storage and other factors on biofilm formation and contamination of patient-ready endoscopes: a narrative review. Gastrointest. Endosc. 91 (2), 236–247. https://doi.org/10.1016/j.gie.2019.08.043.

Alomari, M.M.M., Dec, M., Urban-Chmiel, R., 2021. Bacteriophages as an alternative method for control of zoonotic and foodborne pathogens. Viruses 13 (12), 2348.

Alonso, M., Escribano, P., Guinea, J., Recio, S., Simon, A., Peláez, T., Bouza, E., García de Viedma, D., 2012. Rapid detection and identification of Aspergillus from lower respiratory tract specimens by use of a combined probe-high-resolution melting analysis. J. Clin. Microbiol. 50 (10), 3238–3243.

Anderson, J.G., et al., 2000. Inactivation of food-borne enteropathogenic bacteria and spoilage fungi using pulsed-light. IEEE Trans. Plasma Sci. 28 (1), 83–88. https://doi.org/10.1109/27.842870.

Armstrong-James, D., Brown, G.D., Netea, M.G., Zelante, T., Gresnigt, M.S., van de Veerdonk, F.L., Levitz, S.M., 2017. Immunotherapeutic approaches to treatment of fungal diseases. Lancet Infect. Dis. 17 (12), e393–e402.

Assress, H.A., Selvarajan, R., Nyoni, H., et al., 2021. Antifungal azoles and azole resistance in the environment: current status and future perspectives—a review. Rev. Environ. Sci. Biotechnol. 20, 1011–1041. https://doi.org/10.1007/s11157-021-09594-w.

Bache, S.E., Maclean, M., MacGregor, S.J., Anderson, J.G., Gettinby, G., Coia, J.E., Taggart, I., 2012. Clinical studies of the high-intensity narrow-spectrum light environmental decontamination system (HINS-light EDS), for continuous disinfection in the burn unit inpatient and outpatient settings. Burns 38 (1), 69–76.

Barnes, R.A., 2008. Early diagnosis of fungal infection in immunocompromised patients. J. Antimicrob. Chemother. 61 (Suppl. 1), i3–i6.

Bava, R., Fabio, C., Cristian, P., Vincenzo, M., Carmine, L., Ernesto, P., Domenic, B., Vincenzo, M., 2022. Entomopathogenic fungi for pests and predators control in beekeeping. Vet. Sci. 9 (2), 95. https://doi.org/10.3390/vetsci9020095.

Benkő, R., Gajdács, M., Matuz, M., Bodó, G., Lázár, A., Hajdú, E., Papfalvi, E., Hannauer, P., Erdélyi, P., Pető, Z., 2020. Prevalence and antibiotic resistance of ESKAPE pathogens isolated in the Emergency Department of a Tertiary Care Teaching Hospital in Hungary: a 5-year retrospective survey. Antibiotics (Basel) 9 (9).

Beveridge, J.R., et al., 2002. Comparison of the effectiveness of biphase and monophase rectangular pulses for the inactivation of micro-organisms using pulsed electric fields. IEEE Trans. Plasma Sci. 30 (4), 1525–1531. https://doi.org/10.1109/TPS.2002.804204.

Bhagat, J., Singh, N., Nishimura, N., Shimada, Y., 2021. A comprehensive review on environmental toxicity of azole compounds to fish. Chemosphere 262. https://doi.org/10.1016/j.chemosphere.2020.128335.

Billmyre, R.B., Applen Clancey, S., Li, L.X., Doering, T.L., Heitman, J., 2020. 5-Fluorocytosine resistance is associated with hypermutation and alterations in capsule biosynthesis in Cryptococcus. Nat. Commun. 11 (1), 1–9.

Bongomin, F., Gago, S., Oladele, R.O., Denning, D.W., 2017. Global and multi-national prevalence of fungal diseases—estimate precision. J.Fungi 3 (4), 57.

Brack, W., Barcelo Culleres, D., Boxall, A.B.A., Budzinski, H., Castiglioni, S., Covaci, A., Dulio, V., Escher, B.I., Fantke, P., Kandie, F., Fatta-Kassinos, D., Hernández, F.J., Hilscherová, K., Hollender, J., Hollert, H., Jahnke, A., Kasprzyk-Hordern, B., Khan, S.J., Kortenkamp, A., Kümmerer, K., Lalonde, B., Lamoree, M.H., Levi, Y., Lara Martín, P.A., Montagner, C.C., Mougin, C., Msagati, T., Oehlmann, J., Posthuma, L., Reid, M., Reinhard, M., Richardson, S.D., Rostkowski, P., Schymanski, E., Schneider, F., Slobodnik, J., Shibata, Y., Snyder, S.A., Fabriz Sodré, F., Teodorovic, I., Thomas, K.V., Umbuzeiro, G.A., Viet, P.H., Yew-Hoong, K.G., Zhang, X., Zuccato, E., 2022. One planet: one health. A call to support the initiative on a global science–policy body on chemicals and waste. Environ. Sci. Eur. 34 (1), 21.

Bradley, D., et al., 2012. Studies on the pathogenesis and survival of different culture forms of Listeria monocytogenes to pulsed UV-light irradiation after exposure to mild-food processing stresses. Food Microbiol. 30 (2), 330–339. https://doi.org/10.1016/j.fm.2011.12.024.

Broom, A., Kenny, K., Prainsack, B., Broom, J., 2021. Antimicrobial resistance as a problem of values? Views from three continents. Crit. Public Health 31 (4), 451–463.

Cameron, A., Barbieri, R., Read, R., Church, D., Adator, E.H., Zaheer, R., McAllister, T.A., 2019. Functional screening for triclosan resistance in a wastewater metagenome and isolates of Escherichia coli and Enterococcus spp. from a large Canadian healthcare region. PLoS One 14 (1), e0211144.

Casalini, G., Giacomelli, A., Ridolfo, A., Gervasoni, C., Antinori, S., 2021. Invasive fungal infections complicating COVID-19: a narrative review. J.Fungi 7 (11), 921.

Chen, Z.F., Ying, G.G., 2015. Occurrence, fate and ecological risk of five typical azole fungicides as therapeutic and personal care products in the environment: a review. Environ. Int. 84, 142–153.

Chen, J., Loeb, S., Kim, J.-H., 2017. LED revolution: fundamentals and prospects for UV disinfection applications. Environ. Sci.: Water Res. Technol. 3 (2), 188–202.

Chen, Y., Neff, M., McEvoy, B., Cao, Z., Pezzoli, R., Murphy, A., Gately, N., Hopkins Jnr, M., Rowan, N.J., Devine, D.M., 2019. 3D printed polymers are less stable than injected moulded counterparts when exposed to terminal processes using novel vaporized hydrogen peroxide and electron beam processes. Polymer 183. https://doi.org/10.1016/polymer.2019.121870.

Chen, B., Han, J., Dai, H., Jia, P., 2021. Biocide-tolerance and antibiotic-resistance in community environments and risk of direct transfers to humans: unintended consequences of community-wide surface disinfecting during COVID-19? Environ. Pollut. 283, 117074.

Clancy, C.J., Nguyen, M.H., 2013. Finding the "missing 50%" of invasive candidiasis: how nonculture diagnostics will improve understanding of disease spectrum and transform patient care. Clin. Infect. Dis. 56 (9), 1284–1292.

Fitzhenry, K., et al., 2019. Inactivation efficiency of Bacillus endospores via modified flow-through PUV treatment with comparison to conventional LPUV treatment. J. Water Process Eng. 27, 67–76. https://doi.org/10.1016/j.jwpe.2018.11.009.

Food and Drug, A., 1994. '21 Code of Federal Regulations', Part 21 Current Good Manufacturing Practice for Finished Pharmaceuticals United State.

World Health, O., 2019. Global Antimicrobial Resistance Surveillance System (GLASS): early implementation protocol for inclusion of Candida spp. WHO/WSI/AMR/2019.4).World Health Organization, Geneva Available at https://apps.who.int/iris/handle/10665/326926.

World Health, O., 2020. First Meeting of the WHO Antifungal Expert Group on Identifying Priority Fungal Pathogens: Meeting Report.

Dalgaard, L.S., Nørgaard, M., Povlsen, J.V., Jespersen, B., Jensen-Fangel, S., Ellermann-Eriksen, S., Østergaard, L., Schønheyder, H.C., Søgaard, O.S., 2016. Risk and prognosis of bacteremia and fungemia among peritoneal dialysis patients: a population-based cohort study. Perit. Dial. Int. 36 (6), 647–654.

Dannaoui, E., 2017. Antifungal resistance in mucorales. Int. J. Antimicrob. Agents 50 (5), 617–621.

Dehghani, M.H., Mahvi, A.H., Jahed, G.R., Sheikhi, R., 2007. Investigation and evaluation of ultrasound reactor for reduction of fungi from sewage. J. Zhejiang Univ. Sci. B 8 (7), 493–497.

Domegan, C., 2021. Social marketing and behavioural change in a systems setting. Curr.Opin. Environ.Sci.Health 23, 100275.

Dutescu, I.A., 2021. The antimicrobial resistance crisis: how neoliberalism helps microbes dodge our drugs. Int. J. Health Serv. 51 (4), 521–530.

Etienne, M., Caron, F., 2007. Management of fungal urinary tract infections. Presse Med. 36 (12 Pt 3), 1899–1906.

Farrell, H., Garvey, M., Rowan, N., 2009. Studies on the inactivation of medically important Candida species on agar surfaces using pulsed light. FEMS Yeast Res. 9 (6), 956–966.

Farrell, H., Hayes, J., Laffey, J., Rowan, N., 2011. Studies on the relationship between pulsed UV light irradiation and the simultaneous occurrence of molecular and cellular damage in clinically-relevant Candida albicans. J. Microbiol. Methods 84 (2), 317–326.

Firacative, C., 2020. Invasive fungal disease in humans: are we aware of the real impact? Mem. Inst. Oswaldo Cruz 115.

Fisher, M.C., Alastruey-Izquierdo, A., Berman, J., Bicanic, T., Bignell, E.M., Bowyer, P., Bromley, M., Brüggemann, R., Garber, G., Cornely, O.A., 2022. Tackling the emerging threat of antifungal resistance to human health. Nat. Rev. Microbiol. 1–15.

Fosses Vuong, M., Waymack, J.R., 2022. 'Aspergillosis', StatPearls. StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC, Treasure Island (FL).

Founou, R.C., Founou, L.L., Essack, S.Y., 2017. Clinical and economic impact of antibiotic resistance in developing countries: a systematic review and meta-analysis. PLoS One 12 (12), e0189621.

Franssen, F., Gerard, C., Cozma-Petruţ, A., Vieira-Pinto, M., Jambrak, A.R., Rowan, N., Paulsen, P., Rozycki, M., Tysnes, K., Rodriguez-Lazaro, D., 2018. Inactivation of parasite transmission stages: efficacy of treatments on food of animal origin. Trends Food Sci. Technol. 83 (114–128).

Galanakis, C.M., Rizou, M., Aldawoud, T.M.S., Ucak, I., Rowan, N.J., 2021. Innovations and technology disruptions in the food sector within the COVID-19 pandemic and post-lockdown era. Trends Food Sci. Technol. 110, 193–200.

Galia, L., Pezzani, M.D., Compri, M., Callegari, A., Rajendran, N.B., Carrara, E., Tacconelli, E., Network, C.M.E.-N., 2022. Surveillance of antifungal resistance in candidemia fails to inform antifungal stewardship in European countries. J.Fungi 8 (3), 249.

Garey, K.W., Rege, M., Pai, M.P., Mingo, D.E., Suda, K.J., Turpin, R.S., Bearden, D.T., 2006. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. Clin. Infect. Dis. 43 (1), 25–31.

Garnier, L., Valence, F., Mounier, J., 2017. Diversity and control of spoilage fungi in dairy products: an update. Microorganisms 5 (3), 42.

Garvey, M., et al., 2015a. Pulsed ultraviolet light inactivation of *Pseudomonas aeruginosa* and *Staphylococcus aureus* biofilms. Water Environ. J. 29 (1), 36–42. https://doi.org/10.1111/wej.12088.

Garvey, M., 2020. Bacteriophages and the one health approach to combat multidrug resistance: is this the way? Antibiotics (Basel) 9 (7).

Garvey, M., 2022. Lameness in dairy cow herds: disease aetiology, prevention and management. Dairy 3 (1).

Garvey, M., Cormican, M., Rowan, N., 2010. Investigations of the relationship between use of in vitro cell culture-quantitative PCR and a mouse-based bioassay for evaluating critical factors affecting the disinfection performance of pulsed UV light for treating Cryptosporidium parvum oocysts in saline. J. Microbiol. Methods 80 (3), 267–273. https://doi.org/10.1016/j.mimet.2010.01.017.

Garvey, M., Hayes, J., Clifford, E., Kirf, D., Rowan, N., 2013. Efficacy of measuring cellular ATP levels to determine the inactivation of pulsed UV treated Cryptosporidium parvum oocysts suspended in water. Water Sci. Technol. Water Supply 13 (2), 202–213.

Garvey, M., Andrade Fernandes, J.P., Rowan, N., 2015b. Pulsed light for the inactivation of fungal biofilms of clinically important pathogenic Candida species. Yeast 32 (7), 533–540.

Garvey, M., Rowan, N., 2015. A pulsed light system for the disinfection of flow through water in the presence of inorganic contaminants. J. Water Health 13 (2), 406–412. https://doi.org/10.2166/wh.2014.176.

Gehlot, P., Singh, J., 2018. Fungi and Their Role in Sustainable Development: Current Perspectives. Springer.

Gikas, G.D., Paraskevas, P., Theodoros, M., Zisis, V., 2022. Particularities of fungicides and factors affecting their fate and removal efficacy: a review. Sustainability 14 (7), 4056. https://doi.org/10.3390/su14074056.

Giles, C., Lamont-Friedrich, S.J., Michl, T.D., Griesser, H.J., Coad, B.R., 2018. The importance of fungal pathogens and antifungal coatings in medical device infections. Biotechnol. Adv. 36 (1), 264–280.

Gómez-López, V.M., Bolton, J.R., 2016. An approach to standardize methods for fluence determination in bench-scale pulsed light experiments. Food Bioprocess Technol. 9 (6), 1040–1048.

Gómez-López, V.M., et al., 2022. Guidelines on reporting treatment conditions for emerging technologies in food processing. Crit. Rev. Food Sci. Nutr. 62 (21), 5925–5949. https://doi.org/10.1080/10408398.2021.1895058.

Górski, A., Bollyky, P.L., Przybylski, M., Borysowski, J., Międzybrodzki, R., Jończyk-Matysiak, E., Weber-Dąbrowska, B., 2019. Perspectives of phage therapy in non-bacterial infections. Front. Microbiol. 9.

Hayes, J.C., Garvey, M., Fogarty, A., Clifford, E., Rowan, N., 2012a. Inactivation of recalcitrant protozoan oocysts and bacterial endospores in drinking water using high-intensity pulsed UV light irradiation. Water Supply 12 (4), 513–522. https://doi.org/10.2166/ws.2012.017.

Hayes, J., Kirf, D., Garvey, M., Rowan, N., 2013. Disinfection and toxicological assessments of pulsed UV and pulsed-plasma gas-discharge treated-water containing the waterborne protozoan enteroparasite Cryptosporidium parvum. J. Microbiol. Methods 94 (3), 325–337.

Hayes, J.C., Laffey, J.G., McNeill, B., Rowan, N.J., 2012b. Relationship between growth of food-spoilage yeast in high-sugar environments and sensitivity to high-intensity pulsed UV light irradiation. Int. J. Food Sci. Technol. 47 (9), 925–934. https://doi.org/10.1111/j.1365-2621.2012.03052.x.

Heard, K.L., Hughes, S., Mughal, N., Moore, L.S.P., 2020. COVID-19 and fungal superinfection. The Lancet. Microbe 1 (3), e107.

Heinrich, V., Zunabovic, M., Bergmair, J., Kneifel, W., Jaeger, H., 2015. Post-packaging application of pulsed light for microbial decontamination of solid foods: a review. Innov.Food Sci. Emerg. Technol. 30, 145–156.

Helweg-Larsen, J., Benfield, T., Kovacs, J., Masur, H., 2017. Drug resistance in Pneumocystis jirovecii. Antimicrobial Drug Resistance. Springer, pp. 1147–1162.

Hillock, N.T., Merlin, T.L., Turnidge, J., Karnon, J., 2022. Modelling the future clinical and economic burden of antimicrobial resistance: the feasibility and value of models to inform policy. Appl. Health Econ. Health Policy 1–8.

Hodzic, E., 2015. Lyme borreliosis: is there a preexisting (natural) variation in antimicrobial susceptibility among Borrelia burgdorferi strains? Bosnian J.Basic Med.Sci. 15 (3), 1–13.

Hoenigl et al., n.d. M. Hoenigl M. Levitz Stuart N. Schuetz Audrey X. Zhang Sean A. Cornely Oliver 'All You Need to Know and More about the Diagnosis and Management of Rare Mold Infections', mBio, 12(1), pp. e02920-20.n.d.

Houšť, J., Spížek, J., Havlíček, V., 2020. Antifungal drugs. Metabolites 10 (3), 106.

Huang, T., Zhao, Y., He, J., Cheng, H., Martyniuk, C., 2022. Endocrine disruption by azole fungicides in fish: a rview of he evidence. Sci. Total Environ. 822. https://doi.org/10.1016/j.scitotenv.2022.153412.

Hyde, K.D., 2022. The numbers of fungi. Fungal Divers. 114, 1. https://doi.org/10.1007/s13225-022-00507-y.

Ibáñez-Martínez, E., Ruiz-Gaitán, A., Pemán-García, J., 2017. Update on the diagnosis of invasive fungal infection. Rev.Esp.Quimioterapia 30.

Iyer, K.R., Revie, N.M., Fu, C., Robbins, N., Cowen, L.E., 2021. Treatment strategies for cryptococcal infection: challenges, advances and future outlook. Nat. Rev. Microbiol. 19 (7), 454–466.

Jamali, H., Radmehr, B., Ismail, S., 2014. Prevalence and antibiotic resistance of Staphylococcus aureus isolated from bovine clinical mastitis. J. Dairy Sci. 97 (4), 2226–2230.

Jankowska, K.I., Nagarkatti, R., Acharyya, N., Dahiya, N., Stewart, C.F., Macpherson, R.W., Wilson, M.P., Anderson, J.G., MacGregor, S.J., Maclean, M., 2020. Complete inactivation of blood borne pathogen Trypanosoma cruzi in stored human platelet concentrates and plasma treated with 405 nm violet-blue light. Front.Med. 7, 617373.

Jarvis, J.N., Leeme, T.B., Molefi, M., Chofle, A.A., Bidwell, G., Tsholo, K., Tlhako, N., Mawoko, N., Patel, R.K.K., Tenforde, M.W., Muthoga, C., Bisson, G.P., Kidola, J., Changalucha, J., Lawrence, D., Jaffar, S., Hope, W., Molloy, S.L.F., Harrison, T.S., 2019. Short-course high-dose liposomal amphotericin B for human immunodeficiency virus–associated cryptococcal meningitis: a phase 2 randomized controlled trial. Clin. Infect. Dis. 68 (3), 393–401.

Jørgensen, L.N., Heick, T.M., 2021. Azole use in agriculture, horticulture, and wood preservation–is it indispensable? Front. Cell. Infect. Microbiol. 806.

Josephs-Spaulding, J., Singh, O.V., 2021. Medical device sterilization and reprocessing in the era of multidrug-resistant (MDR) bacteria: issues and regulatory concepts. Front.Med. Technol. https://doi.org/10.3389/fmedt.2020.587352.

Kahhonen, E., Nordstron, K., 2008. Toward a nontoxic posion: current trends in (European Uniion) biocides regulation. Integr. Environ. Assess. Manag. 4 (4), 471–477.

Kalińska, A., Gołębiewski, M., Wójcik, A., 2017. Mastitis pathogens in dairy cattle - a review. World Sci.News 89, 22–31.

Kang, M.H., Pengkit, A., Choi, K., Jeon, S.S., Choi, H.W., Shin, D.B., Choi, E.H., Uhm, H.S., Park, G., 2015. Differential inactivation of fungal spores in water and on seeds by ozone and arc discharge plasma. PloS one 10 (9), e0139263.

Kaplan, J.E., Benson, C., Holmes, K.K., Brooks, J.T., Pau, A., Masur, H., 2009. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm. Rep. 58 (Rr-4), 1–207 quiz CE1-4.

Kauffman, C.A., 2014. Diagnosis and management of fungal urinary tract infection. Infect. Dis. Clin. 28 (1), 61–74.

Kauffman, C.A., Yoshikawa, T.T., 2001. Fungal infections in older adults. Clin. Infect. Dis. 33 (4), 550–555.

Kazemzadeh-Narbat, M., Cheng, H., Chabok, R., Alvarez, M.M., de la Fuente-Nunez, C., Phillips, K.S., Khademhosseini, A., 2021. Strategies for antimicrobial peptide coatings on medical devices: a review and regulatory science perspective. Crit. Rev. Biotechnol. 41 (1), 94–120.

Kim, D.K., Kim, S.J., Kang, D.H., 2017. Bactericidal effect of 266 to 279nm wavelength UVC-LEDs for inactivation of Gram positive and Gram negative foodborne pathogenic bacteria and yeasts. Food Res. Int. 97, 280–287.

Kirby, A., Herbert, A., 2013. Correlations between income inequality and antimicrobial resistance. PLoS One 8 (8), e73115.

Kwakman, J.A., Erler, N.S., Vos, M.C., Bruno, M.J., 2022. Risk evaluatio of dudenoscope-associated infections in the Netherlands calls for a heightened awareness of device-related infection:a systematic review. Endoscopy 54 (02), 148–2022.

Lachapelle, J.-M., Castel, O., Casado, A.F., Leroy, B., Micali, G., Tennstedt, D., Lambert, J., 2013. Antiseptics in the era of bacterial resistance: a focus on povidone iodine. Clin. Pract. 10 (5), 579.

Laso, J., et al., 2022. Achieving sustainability of the seafood sector in the European Atlantic area by addressing eco-social challenges: the NEPTUNUS project. Sustainability 14 (5). https://doi.org/10.3390/su14053054.

Lass-Flörl, C., Samardzic, E., Knoll, M., 2021. Serology anno 2021—fungal infections: from invasive to chronic. Clin. Microbiol. Infect. 27 (9), 1230–1241.

Latgé, J.P., Chamilos, G., 2019. Aspergillus fumigatus and Aspergillosis in 2019. Clin. Microbiol. Rev. 33 (1).

Lee, S.M., Cho, Y.K., Sung, Y.M., Chung, D.H., Jeong, S.H., Park, J.W., Lee, S.P., 2015. A case of pneumonia caused by Pneumocystis jirovecii resistant to trimethoprim-sulfamethoxazole. Korean J. Parasitol. 53 (3), 321–327.

Lee, Y., Puumala, E., Robbins, N., Cowen, L.E., 2020. Antifungal drug resistance: molecular mechanisms in Candida albicans and beyond. Chem. Rev. 121 (6), 3390–3411.

Leidner, F., Kurt Yilmaz, N., Schiffer, C.A., 2021. Deciphering antifungal drug resistance in Pneumocystis jirovecii DHFR with molecular dynamics and machine learning. J. Chem. Inf. Model. 61 (6), 2537–2541.

Lengerova, M., Racil, Z., Hrncirova, K., Kocmanova, I., Volfova, P., Ricna, D., Bejdak, P., Moulis, M., Pavlovsky, Z., Weinbergerova, B., Toskova, M., Mayer, J., 2014. Rapid detection and identification of mucormycetes in bronchoalveolar lavage samples from immunocompromised patients with pulmonary infiltrates by use of high-resolution melt analysis. J. Clin. Microbiol. 52 (8), 2824–2828.

Levinskaite, L., 2012. Susceptibility of food-contaminating Penicillium genus fungi to some preservatives and disinfectants. Ann. Agric. Environ. Med. 19 (1), 85–89.

Li, H., Huang, H., He, H., 2016. Successful treatment of severe pneumocystis pneumonia in an immunosuppressed patient using caspofungin combined with clindamycin: a case report and literature review. BMC Pulm.Med. 16 (1), 1–6.

Lortholary, O., Renaudat, C., Sitbon, K., Desnos-Ollivier, M., Bretagne, S., Dromer, F., 2017. The risk and clinical outcome of candidemia depending on underlying malignancy. Intensive Care Med. 43 (5), 652–662.

Lu, R., Hollingsworth, C., Qiu, J., Wang, A., Hughes, E., Xin, X., Konrath, K.M., Elsegeiny, W., Park, Y.-D., Atakulu, L., Craft, J.C., Tramont, E.C., Mannino, R., Williamson, P.R., 2019. Efficacy of oral encochleated amphotericin B in a mouse model of cryptococcal meningoencephalitis. mBio 10 (3), e00724-19.

Maclean, M., MacGregor, S.J., Anderson, J.G., Woolsey, G., 2009. Inactivation of bacterial pathogens following exposure to light from a 405-nanometer light-emitting diode array. Appl. Environ. Microbiol. 75 (7), 1932–1937.

MacGregor, S.J., et al., 2000. Inactivation of pathogenic and spoilage microorganisms in a test liquid using pulsed electric fields. IEEE Trans. Plasma Sci. 28 (1), 144–149. https://doi.org/10.1109/27.842887.

MacLean, M., Booth, M.G., Anderson, J.G., MacGregor, S.J., Woolsey, G.A., Coia, J.E., Hamilton, K., Gettinby, G., 2013. Continuous decontamination of an intensive care isolation room during patient occupancy using 405 nm light technology. J. Infect. Prev. 14 (5), 176–181.

MacNeill, A., et al., 2020. Transforming the medical device industry: road map to a circular economy. Health Aff. 39 (9), 2088–2097.

Marchese, V., Di Carlo, D., Fazio, G., Gioe, S.M., Luca, A., Alduino, R., Rizzo, M., Tuzzolino, F., Monaco, F., Conaldi, P.G., Douradinha, B., Di Martino, G., 2021. Microbiological surveillance of endoscopes in a southern Italian transplantation hospital: a retrospective study from 2016 to 2019. Int. J. Environ. Res. Public Health 18 (6). https://doi.org/10.3390/ijerph18063057.

Martinez-Rossi, N.M., Bitencourt, T.A., Peres, N.T.A., Lang, E.A.S., Gomes, E.V., Quaresemin, N.R., Martins, M.P., Lopes, L., Rossi, A., 2018. Dermatophyte resistance to antifungal drugs: mechanisms and prospectus. Front. Microbiol. 9, 1108.

Maskarinec, S.A., Johnson, M.D., Perfect, J.R., 2016. Genetic susceptibility to fungal infections: what is in the genes? Curr.Clin.Microbiol.Rep. 3 (2), 81–91.

Massei, R., Busch, W., Wolschke, H., Schinkel, L., Bitsch, M., Schulze, T., Krauss, M., Brack, W., 2018. Screening of pesticide and biocide patterns as risk drivers in sediments of major European river mouths: ubiquitous or river basin-specific contamination? Environ. Sci. Technol. 52 (4), 2251–2260.

Masterson, K., Meade, E., Garvey, M., Lynch, M., Major, I., Rowan, N.J., 2021. Development of a low-temperature extrusion process for production of GRAS bioactive-polymer loaded compounds for targeting antimicrobial-resistant (AMR) bacteria. Sci. Total Environ. 800, 149545.

Matumba, L., Namaumbo, S., Ngoma, T., Meleke, N., De Boevre, M., Logrieco, A.F., De Saeger, S., 2021. Five keys to prevention and control of mycotoxins in grains: a proposal. Glob. Food Secur. 30, 100562.

McEvoy, B., Rowan, N.J., 2019. Terminal sterilization of medical devices using vaporized hydrogen peroxide: a review of current methods and emerging opportunities. J. Appl. Microbiol. 127 (5), 1403–1420.

McEvoy, B., Lynch, M., Rowan, N.J., 2021. Opportunities for the application of real-time bacterial cell analysis using flow cytometry for the advancement of sterilization microbiology. J. Appl. Microbiol. 130 (6), 1794–1812.

Meade, E., Rawe, S., Slattery, M.A., Garvey, M., 2019. An assessment of alternative therapeutic options for the treatment of prolonged zoonotic fungal infections in companion animals. J. Microbiol. Biotechnol. 4, 000149.

Meade, E., Fowley, C., Savage, M., Slattery, M.A., Garvey, M., 2020a. Antibacterial activity of Roussin's black salt against multidrug resistant zoonotic pathogens isolated from companion animals. Acta Sci.Vet.Sci. 2 (3).

Meade, E., Savage, M., Slattery, M.A., Garvey, M., 2020. Disinfection of mycotic species isolated from cases of bovine mastitis showing antifungal resistance. Cohesive J. Microbiol. Infect. Dis. 3.

Meade, E., Savage, M., Garvey, M., 2021. Effective antimicrobial solutions for eradicating multi-resistant and β-lactamase-producing nosocomial gram-negative pathogens. Antibiotics 10 (11), 1283.

Meade, E., Savage, M., Slattery, M., Garvey, M., 2021. Investigation of alternative therapeutic and biocidal options to combat antifungal-resistant zoonotic fungal pathogens isolated from companion animals. Infect. Dis. Rep. 13 (2), 348–366.

Meade, E., Slattery, M.A., Garvey, M., 2021. Biocidal resistance in clinically relevant microbial species: a major public health risk. Pathogens (Basel, Switzerland) 10 (5), 598.
Metodiev, K., 2012. Immunodeficiency.
Moorhead, S., Maclean, M., MacGregor, S.J., Anderson, J.G., 2016. Comparative sensitivity of trichophyton and aspergillus conidia to inactivation by violet-blue light exposure. Photomed. Laser Surg. 34 (1), 36–41.
Murphy, E.J., Masterson, C., Rezoagli, E., O'Toole, D., Major, I., Stack, G.D., Lynch, M., Laffey, J.G., Rowan, N.J., 2020a. β-glucan extracts from the same edible shiitake mushroom Lentinus edodes produce differential in-vitro immunomodulatory and pulmonary cyto-protective effects—implications for coronavirus disease (COVID-19) immunotherapies. Sci. Total Environ. 732, 139330.
Murphy, E.J., Rezoagli, E., Pogue, R., et al., Simonassi-Paiva, B., 2021. Immunomodulatory activity of beta-glucana polysaccharides isolated from different species of mushroom - a potential treatment for inflammatory lung conditions. Sci. Total Environ. https://doi.org/10.1016/j.scitotenv.2021.152177.
Murray, I.M.T., Rowan, N.J., McNamee, S., Campbell, K., Fogarty, A.M., 2018. Pulsed light reduces the toxicity of the algal toxin okadaic acid to freshwater crustacean Daphnia pulex. Environ. Sci. Pollut. Res. Int. 25 (1), 607–614.
Murray, C.J.L., Ikuta, K.S., Sharara, F., Swetschinski, L., Aguilar, G.R., Gray, A., Han, C., Bisignano, C., Rao, P., Wool, E., 2022. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 399 (10325), 629–655.
Nagy, G., Kiss, S., Varghese, R., Bauer, K., Szebenyi, C., Kocsubé, S., Homa, M., Bodai, L., Zsindely, N., 2021. Characterization of three pleiotropic drug resistance transporter genes and their participation in the azole resistance of mucor circinelloides. Front. Cell. Infect. Microbiol. 11, 660347.
Nallal, U.V.M., Razia, M., et al., 2022. Eco-friendly synthesis of multishaped crystalline silver nanoparticles using hill garlic extract and their potential application as an antifungal agent. J. Nanomater. 2022. https://doi.org/10.1155/2022/7613210.
Narayanan, K.B., Park, H.H., 2014. Antifungal activity of silver nanoparticles synthesized using turnip leaf extract (Brassica rapa L.) against wood rotting pathogens. Eur. J. Plant Pathol. 140, 185–192. https://doi.org/10.1007/s10658-014-0399-4.
Nasereddin, Y., 2021. Path to a post-antibiotic world. Sustinere 1 (1), 1–17.
Naughton, J., Tiedeken, E.J., Garvey, M., Stout, J.C., Rowan, N.J., 2017. Pulsed light inactivation of the bumble bee trypanosome parasite Crithidia bombi. J. Apic. Res. 56 (2), 144–154.
Niu, X., Xie, W., Zhang, J., Hu, Q., 2019. Biodiversity of entomopathogenic fungi in the soils of South China. Microorganisms 7 (9), 311. https://doi.org/10.3390/microorganisms7090311.
Nnadi, N.E., Carter, D.A., 2021. Climate change and the emergence of fungal pathogens. PLoS Pathog. 17 (4), e1009503. https://doi.org/10.1371/journal.ppat.1009503.
Nong, G.Y., Liu, Y.-A., Qin, U.-T., Mo, L.-Y., Liang, Y.-P., Zeng, H.H., 2021. Toxc mechanism of three azole fungicides and their mixture of green alga Chlorella pyrenoidosa. Chemosphere 262. https://doi.org/10.1016/j.chemosphere.2020.127793.
Odabasi, Z., Mert, A., 2020. Candida urinary tract infections in adults. World J. Urol. 38 (11), 2699–2707.
O'Neill, E.A., Rowan, N.J., Fogarty, A., 2019. Novel use of the alga Pseudokirchneriella subcapitata, as an early-warning indicator to identify climate change ambiguity in aquatic environments using freshwater finfish farming as a case study. Sci. Total Environ. 692, 209–218.
O'Neill, E.A., McKeon-Bennett, Rowan, N.J., 2022. Peatland-based Innovation can potentially support and enable the Sustainable Development Goals of the United Nations: case study from the Republic of Ireland. Case Stud. Chem. Environ. Eng. (accepted for publication).
Pasquier, E., Kunda, J., De Beaudrap, P., Loyse, A., Temfack, E., Molloy, S.F., Harrison, T.S., Lortholary, O., 2018. Long-term mortality and disability in cryptococcal meningitis: a systematic literature review. Clin. Infect. Dis. 66 (7), 1122–1132.
Pinto, E., Monteiro, C., Maia, M., Faria, M.A., Lopes, V., Lameiras, C., Pinheiro, D., 2018. Aspergillus species and antifungals susceptibility in clinical setting in the north of Portugal: cryptic species and emerging azoles resistance in A. fumigatus. Front. Microbiol. 9, 1656.
Plaza, G., Achal, V., 2020. Biosurfactants: eco-friendly and innovative biocides against biocorrosion. Int. J. Mol. Sci. 21 (6), 2152. https://doi.org/10.3390/ijms21062152.
Powers-Fletcher, M.V., Hanson, K.E., 2016. Nonculture diagnostics in fungal disease. Infect. Dis. Clin. N. Am. 30 (1), 37–49.
Rawson, T.M., Wilson, R.C., Holmes, A., 2021. Understanding the role of bacterial and fungal infection in COVID-19. Clin. Microbiol. Infect. 27 (1), 9–11.
Rehfus, A., Matusinsky, P., Strobel, D., Bryson, R., Stammler, G., 2019. Mutations in target genes of succinate dehydrogenase inhibitors and demethylation inhibitors in Ramularia collo-cygni in Europe. J.Plant Dis.Prot. 126 (5), 447–459.
Rezasoltani, S., Yadegar, A., Hatami, B., Asadzadeh Aghdaei, H., Zali, M.R., 2020. Antimicrobial resistance as a hidden menace lurking behind the COVID-19 outbreak: the global impacts of too much hygiene on AMR. Front. Microbiol. 11.
Romero, M., Messina, F., Marin, E., Arechavala, A., Depardo, R., Walker, L., Negroni, R., Santiso, G., 2019. Antifungal resistance in clinical isolates of Aspergillus spp.: when local epidemiology breaks the norm. J.Fungi 5 (2), 41.
Roudbary, M., Kumar, S., Kumar, A., Černáková, L., Nikoomanesh, F., Rodrigues, C.F., 2021. Overview on the prevalence of fungal infections, immune response, and microbiome role in COVID-19 patients. J.Fungi 7 (9), 720.
Rowan, N.J., 2019. Pulsed light as an emerging technology to cause disruption for food and adjacent industries – quo vadis? Trends Food Sci. Technol. 88, 316–332.
Rowan, N.J., 2020. The role of digital technologies in supporting and improving fishery and aquaculture across the supply chain - Quo Vadis? Aquac.Fish. https://doi.org/10.1016/j.aaf.2022.06.003.
Rowan, N.J., Casey, O., 2021. Empower Eco multiactor HUB: a triple helix 'academia-industry-authority' approach to creating and sharing potentially disruptive tools for addressing novel and emerging new Green Deal opportunities under a United Nations Sustainable Development Goals framework. Curr.Opin.Environ.Sci.Health 21, 100254.
Rowan, N.J., Galanakis, C.M., 2020. Unlocking challenges and opportunities presented by COVID-19 pandemic for cross-cutting disruption in agri-food and green deal innovations: Quo Vadis? Sci. Total Environ. 748, 141362.
Rowan, N.J., Laffey, J.G., 2020. Challenges and solutions for addressing critical shortage of supply chain for personal and protective equipment (PPE) arising from coronavirus disease (COVID19) pandemic – case study from the Republic of Ireland. Sci. Total Environ. 725. https://doi.org/10.1016/j.scitotenv.2020.138532.
Rowan, N.J., Laffey, J.G., 2021. Unlocking the surge in demand for personal and protective equipment (PPE) and improvised face coverings arising from coronavirus disease (COVID-19) pandemic – implications for efficacy, re-use and sustainable waste management. Sci. Total Environ. 752. https://doi.org/10.1016/j.scitotenv.2020.142259.
Rowan, N.J., Moral, R.A., 2021. Disposable face masks and reusable face coverings as non-pharmaceutical interventions (NPIs) to prevent transmission of SARS-CoV-2 variants that cause coronavirus disease (COVID-19): role of new sustainable NPI design innovations and predictive mathematical modelling. Sci. Total Environ. 772, 145530.
Rowan, N.J., Johnstone, C.M., McLean, R.C., Anderson, J.G., Clarke, J.A., 1999. Prediction of toxigenic fungal growth in buildings by using a novel modelling system. Appl. Environ. Microbiol. 65 (11), 4814–4821.
Rowan, N.J., Espie, S., Harrower, J., Anderson, J.G., Marsili, L., MacGregor, S.J., 2007. Pulsed-plasma gas-discharge inactivation of microbial pathogens in chilled poultry wash water. J. Food Prot. 70 (12), 2805–2810.
Rowan, N., Pogue, R., 2021. Editorial overview: green new deal era — Current challenges and emerging opportunities for developing sustaining and disruptive innovation. Curr. Opin. Environ. Sci. Health 22. https://doi.org/10.1016/j.coesh.2021.100294.
Rowan, N.J., Valdramidis, V.P., Gómez-López, V.M., 2015. A review of quantitative methods to describe efficacy of pulsed light generated inactivation data that embraces the occurrence of viable but non culturable state microorganisms. Trends Food Sci. Technol. 44 (1), 79–92.
Rowan, N.J., Meade, E., Garvey, M., 2021. Efficacy of frontline chemical biocides and disinfection approahces for inactivating SARS-CoV-2 variants of concern that cause coronavirus disease with the emergence of opportunities for green eco-solutions. Curr.Opin. Environ.Sci.Health 23 10.10.16/j.coesh.2021.100290.
Rowan, N.J., Murray, N., Qiao, Y., O'Neill, E., Clifford, E., Barceló, D., Power, D.M., 2022. Digital transformation of peatland eco-innovations ('Paludiculture'): enabling a paradigm shift towards the real-time sustainable production of 'green-friendly' products and services. Sci. Total Environ. 838, 156328.
Ruiz-Salmon, et al., 2021. Life cycle assessement of fish and seafood products - a review of methodologies and new challenges. Sci. Total Environ. 761. https://doi.org/10.1016/j.scitotenv.2020.144094.
Rutala, W.A., 2019. Disinfection, sterilization, and antisepsis: an overview. Am. J. Infect. Control 47S, A3–A9. https://doi.org/10.1016/j.ajic.2019.01.018 Jun.
Sanglard, D., 2016. Emerging threats in antifungal-resistant fungal pathogens. Front. Med. (Lausanne) 3, 11.
Sauerbrei, A., 2020. Bactericidal and virucidal activity of ethanol and povidone-iodine. Microbiologyopen 9 (9), e1097.
SeyedAlinaghi, S., Karimi, A., Barzegary, A., Pashaei, Z., Afsahi, A.M., Alilou, S., Janfaza, N., Shojaei, A., Afroughi, F., Mohammadi, P., Soleimani, Y., Nazarian, N., Amiri, A., Tantuoyir, M.M., Oliaei, S., Mehraeen, E., Dadras, O., 2022. Mucormycosis infection in patients with COVID-19: a systematic review. Health Sci. Rep. 5 (2), e529.
Silva, E.R., et al., 2019. Eco-friendly non-biocide release coatings for marine biofouling prevention. Sci. Total Environ. https://doi.org/10.1016/j.scitotenv.2018.10.010.
Skiada, A., Pavleas, I., Drogari-Apiranthitou, M., 2020. Epidemiology and diagnosis of mucormycosis: an update. J. Fungi (Basel) 6 (4).
Sousa, F., Ferreira, D., Reis, S., Costa, P., 2020. Current insights on antifungal therapy: novel nanotechnology approaches for drug delivery systems and new drugs from natural sources. Pharmaceuticals 13 (9), 248.
Stone, N., Gupta, N., Schwartz, I., 2021. Mucormycosis: time to address this deadly fungal infection. Lancet Microbe 2 (8), e343–e344.
Suanda, J., Suanda, J., Cawley, D., Domegan, C., Brenner, M., Rowan, N., 2013. A review of the perceived barriers within the health belief model on pap smear screening as a cervical cancer prevention measure. J.Appl.Sci.Res. 3.
Sun, Y., Meng, F., Han, M., Zhang, X., Yu, L., Huang, H., Wu, D., Ren, H., Wang, C., Shen, Z., Ji, Y., Huang, X., 2015. Epidemiology, management, and outcome of invasive fungal disease in patients undergoing hematopoietic stem cell transplantation in China: a multicenter prospective observational study. Biol. Blood Marrow Transplant. 21 (6), 1117–1126.
Taccone, F.S., Van den Abeele, A.M., Bulpa, P., Misset, B., Meersseman, W., Cardoso, T., Paiva, J.A., Blasco-Navalpotro, M., De Laere, E., Dimopoulos, G., Rello, J., Vogelaers, D., Blot, S.I., 2015. Epidemiology of invasive aspergillosis in critically ill patients: clinical presentation, underlying conditions, and outcomes. Crit. Care 19 (1), 7.
Tiedeken, E.J., Tahar, A., McHugh, B., Rowan, N.J., 2017. Monitoring, sources, receptors, and control measures for three European Union watch list substances of emerging concern in receiving waters - a 20 years systematic review. Sci. Total Environ. 574, 1140–1163.
Truong, J., Ashurst, J.V., 2022. 'Pneumocystis Jirovecii Pneumonia', StatPearls. StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC, Treasure Island (FL).
Trzaska, W.J., Wrigley, H.E., Thwaite, J.E., May, R.C., 2017. Species-specific antifungal activity of blue light. PubMedSci. Reports 7 (1), 4605. https://doi.org/10.1038/s41598-017-05000-0 (Accessed 2017/07//).
Valencia-Shelton, F., Loeffelholz, M., 2014. Nonculture techniques for the detection of bacteremia and fungemia. Future Microbiol. 9 (4), 543–559.
Vallabhaneni, S., Mody, R.K., Walker, T., Chiller, T., 2016. The global burden of fungal diseases. Infect. Dis. Clin. 30 (1), 1–11.
van der Linden, J.W.M., Camps, S.M.T., Kampinga, G.A., Arends, J.P.A., Debets-Ossenkopp, Y.J., Haas, P.J.A., Rijnders, B.J.A., Kuijper, E.J., van Tiel, F.H., Varga, J., 2013. Aspergillosis due to voriconazole highly resistant Aspergillus fumigatus and recovery of genetically related resistant isolates from domiciles. Clin. Infect. Dis. 57 (4), 513–520.
van der Poll, T., van de Veerdonk, F.L., Scicluna, B.P., Netea, M.G., 2017. The immunopathology of sepsis and potential therapeutic targets. Nat. Rev. Immunol. 17 (7), 407–420.
Verweij, P.E., Lucas, J.A., Arendrup, M.C., Bowyer, P., Brinkmann, A.J.F., Denning, D.W., Dyer, P.S., Fisher, M.C., Geenen, P.L., Gisi, U., Hermann, D., Hoogendijk, A., Kiers, E., Lagrou, K., Melchers, W.J.G., Rhodes, J., Rietveld, A.G., Schoustra, S.E., Stenzel, K.,

Zwaan, B.J., Fraaije, B.A., 2020. The one health problem of azole resistance in Aspergillus fumigatus: current insights and future research agenda. Fungal Biol.Rev. 34 (4), 202–214.
Wan, Q., Wen, G., Cao, R., Xu, X., Zhao, H., Li, K., Wang, J., Huang, T., 2020. Comparison of UV-LEDs and LPUV on inactivation and subsequent reactivation of waterborne fungal spores. Water Res. 173, 115553.
Wang, H., Peng, H., Cheng, P., Gong, M., 2021. The toxins of Beauveria bassiana and the strategies to improve their virulence to insects. Front. Microbiol. 2375.
Wen, X., Chen, Q., Yin, H., Wu, S., Wang, X., 2020. Rapid identification of clinical common invasive fungi via a multi-channel real-time fluorescent polymerase chain reaction melting curve analysis. Medicine 99 (7).
White, T.C., Findley, K., Dawson, T.L., Scheynius, A., Boekhout, T., Cuomo, C.A., Xu, J., Saunders, C.W., 2014. Fungi on the skin: dermatophytes and Malassezia. Cold Spring Harbor Perspect.Med. 4 (8), a019802.
Wiederhold, N.P., 2017. Antifungal resistance: current trends and future strategies to combat. Infect.Drug Resist. 10, 249.
Wüthrich, M., Deepe Jr., G.S., Klein, B., 2012. Adaptive immunity to fungi. Annu. Rev. Immunol. 30, 115.
Xu, S., Zhang, G., Wang, M., Lin, T., Liu, W., Wang, Y., 2022. Phage nanoparticle as a carrier for controlling fungal infection. Appl. Microbiol. Biotechnol. 1–7.
Yaman, M., 2017. Entomopathogen Biodiversity of Kastamonu Region. Kastamonu University Journal of Forestry Faculty, International Forestry Symposium 2016 Special Issue, pp. 368–372 https://doi.org/10.17475/kastorman.293151.
Yousfi, H., Ranque, S., Rolain, J.-M., Bittar, F., 2019. In vitro polymyxin activity against clinical multidrug-resistant fungi. Antimicrob. Resist. Infect. Control 8 (1), 1–10.
Zafar, H., Altamirano, S., Ballou, E.R., Nielsen, K., 2019. A titanic drug resistance threat in Cryptococcus neoformans. Curr. Opin. Microbiol. 52, 158–164.
Zhang, Y., Zhu, Y., Gupta, A., Huang, Y., Murray, C.K., Vrahas, M.S., Sherwood, M.E., Baer, D.G., Hamblin, M.R., Dai, T., 2014. Antimicrobial blue light therapy for multidrug-resistant Acinetobacter baumannii infection in a mouse burn model: implications for prophylaxis and treatment of combat-related wound infections. J. Infect. Dis. 209 (12), 1963–1971.
Zhen, X., Lundborg, C.S., Sun, X., Hu, X., Dong, H., 2019. Economic burden of antibiotic resistance in ESKAPE organisms: a systematic review. Antimicrob.Resist.Infect.Control 8 (1), 137.
Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., Guan, L., Wei, Y., Li, H., Wu, X., Xu, J., Tu, S., Zhang, Y., Chen, H., Cao, B., 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395 (10229), 1054–1062.