Global Burden of Fungal Infections and Antifungal Resistance from 1961 to 2024: Findings and Future Implications

Steward Mudenda

Department of Pharmacy, School of Health Sciences, University of Zambia, Lusaka, Zambia
Email: steward.mudenda@unza.zm

Abstract

Background: Antifungal resistance (AFR) is a global public health problem with devastating effects, especially among immunocompromised individuals. Addressing AFR requires a One Health approach including Antifungal Stewardship (AFS). This study aimed to comprehensively review global studies published on fungal infections and AFR and to recommend solutions to address this growing problem. Materials and Methods: This was a narrative review that was conducted using published papers on fungal infections, AFR, and AFS between January 1961 and March 2024. The literature was searched using PubMed, Google Scholar, Web of Science, and EMBASE. Results: This found that there has been an increase in fungal infections globally, especially among immunocompromised patients. Due to this increase in fungal infections, there has been a proportionate increase in the use of antifungal agents to prevent and treat fungal infections. This increased use of antifungal agents has worsened the problem of AFR contributing to increased morbidity and mortality. Globally, fungal infections have contributed to 150 million infections annually and 1.7 million deaths per year. By the year 2023, over 3.8 million people died from fungal infections. Addressing AFR remains a challenge because the treatment of antifungal-resistant infections is difficult. Finally, the treatment of fungal infections is a global challenge exacerbated by the limited number of antifungal agents to treat invasive fungal infections. Conclusion: The results of this study indicated that fungal infections and AFR are prevalent across humans, animals, agriculture, and the environment. Addressing this problem requires the provision of solutions such as improving the awareness of AFR, conducting further research on the discovery of new antifungal agents, and implementing AFS programs. If this global problem is not addressed, the morbidity and mortality associated with AFR will continue to rise in the future.
1. Introduction

Antifungal resistance (AFR) is a global public health issue [1] [2] [3] [4] [5], that has been exacerbated by the exposure of fungi to antifungal agents and as a result of an increased number of immunocompromised patients [1] [2] [6]. This problem has been worsened by the lack of a variety of antifungal arsenals to treat fungal infections [2] [7] [8]. This phenomenon is a subset of antimicrobial resistance (AMR) which occurs when bacteria, viruses, and protozoa resist or adapt to the lethal effects of antimicrobial drugs [9] [10] [11] [12]. The resistance of microorganisms to antimicrobial drugs may cause negative consequences including increased morbidity, mortality, medical costs, and economic breakdown [9] [13] [14] [15]. If these problems are not addressed, global and regional deaths will continue and worsen in the next decades [16] [17] [18].

The WHO developed a fungal priority pathogens list to help develop strategies to address the growing problem of fungal infections and AFR [19]. Consequently, fungal infections have increased in the recent past, especially among immunocompromised patients [20] [21] [22] [23]. Additionally, systemic fungal infections are often diagnosed late thereby increasing the mortality rate of patients [24] [25]. On top of that, the burden of fungal infections increased during the COVID-19 pandemic leading to increased morbidity and mortality [26]-[34]. An approximate number of 150 million people have been infected with fungal infections annually with approximately 1.7 million deaths reported annually due to fungal infections, indicating the need to address this problem [20]. By the year 2023, more than 6.5 million people had suffered from fungal infections annually of which more than about 3.8 million deaths were recorded [35] [36]. Consequently, the use of antifungal agents has proportionately increased to circumvent fungal infections [37] [38] [39]. It is pertinent to note that AFR is a natural phenomenon where fungi are naturally resistant to certain Antifungal agents [40] [41]. However, the overuse and misuse of antifungal agents have contributed to the development of AFR [37] [39] [41] [42] [43]. Antifungal agents are overused or misused in humans [44] [45], animals [46], agriculture [47] [48], and other environmental sectors [49]. This overuse and misuse have contributed to the occurrence of AFR in the One Health ecosystem [50] [51]. On top of that, like other antimicrobial drugs [52] [53] [54] [55], antifungal agents are widely accessed without prescriptions [56]. Therefore, the inappropriate use of antifungals is a huge burden that magnifies AFR [2] [57] [58], this is similar to reports on the inappropriate use of antibiotics [59] [60] [61] [62].

Evidence has shown that some fungi have developed resistance to antifungal agents and have become resistant to antifungal agents.
agents [63] [64]. The first AFR was reported in 1961 and involved the resistance of dermatophytes to griseofulvin [65]. Some of the mechanisms involved in the resistance of fungi to antifungals include a reduction in the intercellular concentration of the target enzyme, alteration in sterol biosynthesis, overexpression of the antifungal drug target, and alteration in drug target [37]. Examples of fungi that have developed resistance to azoles include Candida species and Aspergillus species [66] [67] [68] [69] [70]. Resistance to echinocandins has also been reported in other studies [66] [71] [72]. Consequently, many fungi species have developed resistance to many of the current antifungal agents thereby making control and treatment of fungal infections difficult or impossible [66] [73]. In turn, this will continue to raise the morbidity and mortality associated with fungal infections [20] [22] [74].

Strategies to address AFR have been documented and require urgent attention just like those implemented to address AMR [14] [66] [75]. Antifungal stewardship (AFS) programs have been reported to be effective in addressing AFR [76]. AFR involves promoting the rational prescribing of antifungal agents, especially only when they are required [77] [78] [79]. Studies have reported an improvement in the prescribing and consumption of antifungals after the implementation of AFS [80] [81]. Therefore, adequate sensitisation and awareness campaigns concerning AFR may help curb this problem [2] [14] [82].

In this paper, a comprehensive narrative review of the global burden of fungal infections and AFR was provided. This review is critical and provides recommendations on the strategies to employ to combat AFR. Therefore, this narrative review comprehensively reviewed global studies published on fungal infections and AFR and recommended solutions for addressing this growing problem.

2. Materials and Methods

This study adopted a narrative review design to collect data on studies published from January 1961 to March 2024. This study used a narrative review design to comprehensively include all studies published on AFR and AFS globally and regionally. Narrative reviews have been reported to be effective in reporting such global issues. Hence, a similar approach from previous studies was adopted [61] [83] [84] [85] [86] [87]. All literature search was done using PubMed, Google Scholar, Web of Science, and EMBASE. The literature involved using words including “antifungal resistance”, “antifungal stewardship”, “antifungals”, “antifungal agents”, “antifungal drugs”, “burden”, AND “fungal infections”. This review included articles that were published between January 1961 to March 2024 on fungal infections, AFR, and AFS. To address the aim of this narrative review, all published studies that focused on the burden of fungal infections and AFR, and strategies to address AFR were included in the study. This provided comprehensive literature that can be built on by other researchers in the future. Additionally, only articles that were published in English were included in this review. This review excluded abstracts and articles not published in English.
3. Results and Discussion

Antifungal resistance (AFR) remains a problem that has been neglected compared to antibacterial and antiviral resistance [58] [73] [76] [88] [89]. This study was conducted to comprehensively provide information on the global and regional studies published on AFR and AFS and provide recommendations to address this problem. The study found that AFR is a growing problem and has been reported globally and regionally across the One Health ecosystem and requires urgent attention. The high resistance of fungi to antifungal agents demonstrates the growing problem of reduced effectiveness of most of these drugs. Addressing AFR requires a One Health approach alongside instigating strategies for the discovery of antifungal agents, implementing AFR, and international collaborations (Table 1).

3.1. Global Burden of Fungal Infections and Associated Mortality

Fungal infections are among the common infections reported in the healthcare

<table>
<thead>
<tr>
<th>Authors and year</th>
<th>Area of research</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO, 2022 [19]</td>
<td>Fungal infections</td>
<td>The WHO classified 19 fungi as priority fungal pathogens and these include Cryptococcus, neoformans, Candida auris, Aspergillus fumigatus, Candida albicans, Nakaseomyces glabrata (Candida glabrata), Histoplasma spp., Eumycetoma causative agents, Mucorales, Fusarium spp., Candida tropicalis, Candida parapsilosis, Scedosporium spp., Lomentospora prolificans, Coccidioides spp., Pichia kudriavzeveii (Candida kruzei), Cryptococcus gattii, Talaromyces marneffei, Pneumocystis jirovecii, and Paracoccidioides spp. Globally, over 6.5 million people suffer from invasive fungal infections annually with more than 2.1 million suffering from invasive aspergillosis, 1.8 million suffering from chronic pulmonary aspergillosis, and over 1.5 million found to have invasive candidiasis or Candida bloodstream infections. A total of 500,000 people were diagnosed with Pneumocystis pneumonia, 194,000 had Cryptococcal meningitis, and 11.5 were affected with fungal asthma. Notably, other life-threatening fungal infections caused 300,000 infections annually. Fungal infections cause approximately 3.8 million deaths annually, with over 2.5 million deaths directly attributed to fungal infections.</td>
</tr>
<tr>
<td>Denning, 2024 [35]</td>
<td>Fungal infections</td>
<td>people were diagnosed with Pneumocystis pneumonia, 194,000 had Cryptococcal meningitis, and 11.5 were affected with fungal asthma. Notably, other life-threatening fungal infections caused 300,000 infections annually. Fungal infections cause approximately 3.8 million deaths annually, with over 2.5 million deaths directly attributed to fungal infections.</td>
</tr>
<tr>
<td>Kanafani and Perfect, 2008 [90]</td>
<td>AFR</td>
<td>AFR is a global public health problem and causes an increase in morbidity and mortality, especially among high-risk populations.</td>
</tr>
<tr>
<td>Pfaller, 2012 [91]</td>
<td>AFR</td>
<td>The overuse and misuse of antifungal agents have contributed to AFR, especially through acquired resistance, across the One Health ecology.</td>
</tr>
<tr>
<td>Kara et al., 2021 [80]</td>
<td>AFS</td>
<td>Instigation of AFS has been demonstrated to promote rational use of antifungal agents.</td>
</tr>
<tr>
<td>Agrawal et al., 2016 [92]</td>
<td>AFS</td>
<td>AFS is essential in addressing AFR and must be implemented in a multidisciplinary approach.</td>
</tr>
<tr>
<td>Vitiello et al., 2023 [2]</td>
<td>Antifungal drug discovery</td>
<td>The discovery of new antifungal agents will be critical in addressing the problem of AFR.</td>
</tr>
<tr>
<td>Vandeputte, Ferrari, and Coste, 2012 [93]</td>
<td>Antifungal drug discovery</td>
<td>The identification and discovery of new antifungal agents can contribute towards addressing AFR.</td>
</tr>
</tbody>
</table>
system, especially among immunocompromised patients. The growing problem of fungal infections prompted the WHO to develop a fungal priority pathogens list to guide research, development and public health action [19] [94]. As shown in Table 1, a total of 19 fungi have been reported to be of public health concern and have been listed under the priority fungal pathogens including Cryptococcus, neoformans, Candida auris, Aspergillus fumigatus, Candida albicans, Nakaseomyces glabrata (Candida glabrata), Histoplasma spp., Eumycetoma causative agents, Mucorales, Fusarium spp., Candida tropicalis, Candida parapsilosis, Scedosporium spp., Lomentospora prolificans, Coccidioides spp., Pichia ku driavzeveii (Candida krusei), Cryptococcus gattii, Talaromyces marneffei, Pneumocystis jirovecii, and Paracoccidioides spp [19] [95]. Global statistics have shown that over 6.5 million people suffer from invasive fungal infections annually [35] [36]. Of the 6.5 million invasive fungal infections, more than 2.1 million had invasive aspergillosis, 1.8 million suffered from chronic pulmonary aspergillosis, and over 1.5 million were found to have invasive candidiasis or Candida bloodstream infections [35]. Consequently, a total of 500,000 people were diagnosed with Pneumocystis pneumonia, 194,000 had Cryptococcal meningitis, and 11.5 were affected with fungal asthma [35]. Finally, other life-threatening fungal infections caused 300,000 infections annually [35].

Fungal infections have been reported to cause approximately 3.8 million deaths annually, which included over 2.5 million deaths directly attributed to fungal infections [35] [36]. Of these deaths, 995,000 were due to chronic pulmonary aspergillosis while 214,000 were due to Pneumocystis pneumonia [35]. Additionally, a total of 147,000 deaths resulted from Cryptococcal meningitis while 46,000 were caused by fungal asthma [35]. Furthermore, other life-threatening fungal infections caused a total of 161,000 deaths annually [35].

A study conducted in Africa, specifically in Zimbabwe, reported that 14.9% of Zimbabweans were annually affected with fungal infections [96]. Fungal infections were prevalent in immunocompromised patients including those suffering from HIV/AIDs, tuberculosis, cancer, chronic obstructive pulmonary disease, and asthma [96].

The burden of fungal infections was worsened during the COVID-19 outbreak [97]-[103]. Consequently, this led to an increase in morbidity and mortality in patients who had COVID-19 and fungal infections [104] [105].

3.2. Treatment of Fungal Infections

The treatment of fungal infections has relied heavily on four major classes of systemically acting antifungal agents including azoles, echinocandins, polyenes, and the pyrimidine analogues [41]. Examples of azoles include fluconazole, isavuconazole, itraconazole, voriconazole, and posaconazole whereas examples of polyenes include conventional amphotericin B and its lipid formulations [38]. Additionally, examples of echinocandins include caspofungin, micafungin, and anidulafungin [38]. An example of a pyrimidine analogue is 5-flucytosine [41]. Of these examples of antifungal drugs, the most used first line of treatment for
Candida species include fluconazole and some echinocandins [106]. However, the treatment of fungal infections is affected by the emergence of drug-resistant fungal infections [67] [106] [107].

3.3. Antifungal Resistance as a Global Public Health Problem

Antifungal resistance (AFR) has been reported as a global public health problem and has been recognized as a significant global public health problem, posing serious threats to human health, agriculture, and the environment [74] [108]. Consequently, AFR can lead to treatment failures, prolonged illnesses, and increased mortality rates. Infections caused by resistant fungi are more difficult to treat, resulting in higher morbidity and mortality rates among affected individuals [4]. On top of that, AFR has economic implications for the patient, healthcare system, and countries [109] [110].

Consequently, the emergence of AFR limits the effectiveness of available antifungal agents [90]. As resistance spreads, the number of effective treatment options decreases, leaving patients with fewer alternatives for managing fungal infections [93]. Evidence has revealed that vulnerable populations, such as those with compromised immune systems (e.g., transplant recipients, HIV/AIDS patients, and cancer patients), are particularly susceptible to fungal infections [96] [111] [112]. AFR disproportionately affects these individuals, leading to increased health disparities [113].

The AFR problem has been magnified by the limited number of new antifungal agents in the manufacturing pipeline compared to antibacterial agents [43] [114]. The challenges in antifungal drug development, coupled with the economic considerations of pharmaceutical companies, contribute to a scarcity of novel antifungal agents [115] [116]. For instance, there are very few antifungal agents used in the treatment of invasive fungal infections compared to antibacterial agents [115]. With this limited number of antifungal agents, the problem of AFR is a huge issue and must be tackled in a One Health approach [40].

Fungal infections are often underdiagnosed, leading to delayed treatment and increased likelihood of resistance development [117]. Lack of awareness among healthcare professionals and the general public about fungal infections and resistance further exacerbates the problem. This challenge has been worsened by the readily availability of antifungal agents [118] [119]. Besides, AFR has been driven by the ease of access to antifungal agents and increased self-medication practices among individuals [120]. AFR is considered a global health security concern [121] [122] [123]. Resistant fungal strains can lead to outbreaks that have the potential to spread rapidly and cause significant public health crises [122] [124].

Concerns about AFR are of public health importance because fungal infections and resistance do not respect national borders [5]. In this case, resistant fungal strains can easily spread across countries and continents, making it a global challenge that requires collaborative efforts to monitor, control, and miti-
Thereupon, AFR imposes a substantial economic burden on healthcare systems. Prolonged hospital stays, increased healthcare costs, and the need for more expensive treatments contribute to the economic impact of resistant fungal infections. Further, AFR in agriculture contributes to crop losses and decreased food production. This not only affects food security but also has economic implications for farmers and the global food supply chain. Furthermore, the use of antifungal agents in agriculture, as well as their discharge into the environment, can lead to the development of resistance in environmental fungi. This poses risks to ecosystems, wildlife, and the overall environmental balance. This indicates that AFR affects the One Health ecosystem and exemplifies the interconnectedness of human health, animal health, and environmental health. A One Health approach, considering the health of humans, animals, and ecosystems, is essential to comprehensively address the issue.

3.4. Examples of Fungi Resistant to Antifungal Agents

Resistance to azoles including fluconazole has increased in recent years due to azoles being overused. A study that was conducted in India revealed that fungi demonstrated a 1.02-fold increase in resistance to voriconazole per year, with Fusarium species having a 1.04-fold increase in resistance to this drug per year. Resistance to azoles has been reported in other studies. Consequently, the resistance of Aspergillus species is a public health problem that requires urgent attention due to its impact on poor treatment outcomes. A common resistance mechanism of Aspergillus fumigatus is a combination of mutations in the gene cyp51A (TR34/L98H). A high resistance of Candida auris to fluconazole was reported during the COVID-19 pandemic in Lebanon. Consequently, Pandrug-resistant Candida auris was reported in the United States indicating that the isolates were resistant to all four classes of antifungal agents.

An Indian study reported that fungi had a 1.06-fold increase in resistance to natamycin, a polyene macrolide, per year, with Fusarium species having a 1.06-fold increase in resistance to this drug. Aspergillus species demonstrated a 1.09-fold increase in resistance while other filamentous fungi exhibited a 1.07-fold increase in resistance to natamycin per annum. Resistance of fungi to other polyene macrolide antifungals including Amphotericin B has also been reported in other studies. A study in the United States also reported high fluconazole-resistant candida species. A study that was conducted in Lebanon among COVID-19 patients demonstrated that all isolates of Candida auris were resistant to Amphotericin B. Consequently, this caused an increase in morbidity and mortality among patients suffering from COVID-19.

The resistance of C. albicans to echinocandins has been reported and said to be due to spontaneous mutations in two hot spot regions of the Fks1 gene in the fungi, this is the target protein of echinocandins which serves to reduce the sen-
sitivity of the enzyme to the echinocandins [72] [144]. Similarly, the resistance of 
C. glabrata to echinocandins has been reported to be due to mutations in the
drug target genes, FKS1 and FSK2 [145]. The resistance of C. glabrata to echi-
ocandins is approximately 3% - 5%, indicating a public health concern and a
need for urgent action to address this issue [146]. The prevalence of C. glabrata
to echinocandins can even reach 10% - 15% [144] [147]. Consequently, the de-
velopment of resistance of C. glabrata to echinocandins has continued to rise
[148]. Some of the examples of fungi that have developed resistance to antifungal
agents are shown in Table 2.

Over the years, fungi have developed resistance to antifungal agents thereby
cauing difficulties in treating fungal infections and consequently increased
morbidity and mortality.

3.5. Strategies to Address Antifungal Resistance

AFR poses a significant threat to global health, necessitating comprehensive
strategies to mitigate its impact including the establishment of robust surveil-
ance systems for monitoring resistance patterns in both clinical and environ-
mental settings [158]. By collecting and analyzing data on AFR, healthcare pro-
fessionals and policymakers can make informed decisions and respond promptly
to emerging challenges [158]. Further, the WHO developed the fungal priority
pathogens list to contribute towards galvanizing fungal infections and AFR by
promoting surveillance, public health interventions, and research and develop-
ment, and innovation [19]. Therefore, there is a need to promote a One Health
approach in addressing fungal infections and AFR [57] [159].

Table 2. Emergence of antifungal drug resistance over the years, 1961-2024.

<table>
<thead>
<tr>
<th>Author, year, citation</th>
<th>Drug-resistant Fungi</th>
<th>Country</th>
<th>Study year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michaelides et al., 1961 [65]</td>
<td>Trichophyton tonsurans</td>
<td>United States</td>
<td>1961</td>
</tr>
<tr>
<td>Khan et al., 2007 [156]</td>
<td>Candida haemulonii</td>
<td>Kuwait</td>
<td>2007</td>
</tr>
<tr>
<td>Satoh et al., 2009 [149]</td>
<td>Candida auris</td>
<td>Japan</td>
<td>2009</td>
</tr>
<tr>
<td>Khan et al., 2007 [156]</td>
<td>Candida haemulonii</td>
<td>Kuwait</td>
<td>2007</td>
</tr>
<tr>
<td>Kim et al., 2009 [157]</td>
<td>Candida haemulonii</td>
<td>Korea</td>
<td>2009</td>
</tr>
<tr>
<td>Pfaller et al., 2011 [152]</td>
<td>Candida species</td>
<td>United States</td>
<td>2010</td>
</tr>
<tr>
<td>Chowdhary et al., 2016 [150]</td>
<td>Candida auris</td>
<td>Korea</td>
<td>2011</td>
</tr>
<tr>
<td>Pfaller et al., 2015 [154]</td>
<td>Candida and Aspergillus species</td>
<td>China</td>
<td>2012</td>
</tr>
<tr>
<td>Sarma et al., 2012 [136]</td>
<td>Candida auris</td>
<td>India</td>
<td>2012</td>
</tr>
<tr>
<td>Chowdhary et al., 2020 [151]</td>
<td>Candida auris</td>
<td>India</td>
<td>2020</td>
</tr>
<tr>
<td>Magnasco et al., 2021 [104]</td>
<td>Candida auris</td>
<td>Italy</td>
<td>2021</td>
</tr>
<tr>
<td>Allaw et al., 2021 [138]</td>
<td>Candida auris</td>
<td>Lebanon</td>
<td>2021</td>
</tr>
<tr>
<td>Xu et al., 2022 [155]</td>
<td>Candida auris</td>
<td>China</td>
<td>2022</td>
</tr>
<tr>
<td>Jacobs et al., 2022 [139]</td>
<td>Candida auris</td>
<td>United States</td>
<td>2022</td>
</tr>
</tbody>
</table>
3.5.1. Antifungal Stewardship Programs, Research and Development, and Improved Diagnostics to Address Antifungal Resistance

Antifungal stewardship (AFS) programs are essential in promoting the rational use of antifungals [78] [92] [160]. The rational use of antifungal agents is paramount in addressing AFR [79]. Therefore, educating and encouraging healthcare workers to adhere to evidence-based guidelines when prescribing antifungals can prevent overuse and misuse, helping to maintain the efficacy of existing medications [161]. On top of that, education and awareness campaigns play a pivotal role in this regard, informing healthcare providers, farmers, and the general public about responsible antifungal use, the risks of resistance, and the importance of compliance with prescribed regimens [2] [14] [82] [162]. AFS programs are critical because they provide training to healthcare workers thereby raising awareness, promoting the rational use of antifungal agents, and reducing the emergence and spread of AFR [161] [163] [164] [165] [166]. The introduction of AFS in hospitals has been reported to reduce the overuse of antifungal agents and improve their rational use while reducing the expenditure associated with their use [77] [167] [168]. Moreover, just like in antibiotic resistance [169]-[177], there is a need to adhere to the antifungal treatment guidelines. Consequently, healthcare facilities must be guided to develop AFS programs to address AFR [79] [81] [178].

There is an urgent need to raise awareness of AFR and predisposing factors. Public health campaigns are essential for engaging individuals in the fight against AFR, as enshrined in the WHO fungal priority pathogens list [19]. By raising awareness about the responsible use of antifungal agents and emphasizing the role of each person in preventing the spread of fungal infections, these campaigns empower communities to actively participate in the collective effort to combat resistance [40].

The WHO fungal priority pathogens list promotes research, development, and innovation in galvanizing AFR [19]. Investing in research and development is crucial to discovering new antifungal agents and developing combination therapies [7] [93] [179] [180] [181]. By diversifying the available treatments and mechanisms of action, the likelihood of resistance can be reduced [182]. Improved diagnostics also play a key role, enabling timely identification of fungal infections and facilitating targeted therapy [183]. The development and deployment of rapid and accurate diagnostic tools, including point-of-care options, PCR, next-generation sequencing, microfluidic chip technology, nanotechnology tools, new-generation biosensors, T2 Candida, and artificial intelligence models are essential components of a comprehensive strategy to address fungal infections and AFR [21] [183] [184] [185]. Nanotechnology has been reported to be a good source of antifungal agents [186]. Therefore, there is a need to promote the use of nanotechnology to address AMR [187] [188].

3.5.2. Restricting Access to Antifungal Agents without a Prescription

Restricting access to antifungal agents without a prescription is a regulatory
measure aimed at promoting responsible use, minimizing overuse, and addressing the growing concern of antifungal resistance [2]. The prescription requirement serves as a reminder to patients about the importance of using antifungal medications responsibly [189]. This includes completing the full course of treatment as prescribed, which is crucial for preventing the development of resistance. Requiring a prescription ensures that individuals consult with healthcare professionals before using antifungal agents. This helps prevent self-diagnosis and self-medication, reducing the risk of inappropriate use and the development of resistance. Additionally, a prescription requirement encourages proper diagnosis of fungal infections by qualified healthcare providers. This is essential for determining the most appropriate antifungal treatment based on the specific type and severity of the infection. Consequently, access restrictions help control the overuse of antifungal agents, which is a significant contributor to the emergence of resistance. Healthcare providers can assess the necessity of antifungal treatment and prescribe it judiciously, avoiding unnecessary exposure to these medications [118].

Restricting access to antifungal agents without a prescription is a proactive measure to address the global challenge of AMR, including AFR [189]. By controlling the distribution of these medications, regulatory authorities can play a role in preserving the effectiveness of existing antifungal agents. Requiring a prescription facilitates healthcare professionals in monitoring patients for potential adverse effects and ensuring appropriate follow-up care. This enhances patient safety and contributes to better overall healthcare outcomes. On top of that, many countries align their healthcare policies with international guidelines that recommend prescription-based access to antimicrobial drugs, including antifungals. Such alignment promotes a unified global effort to address the broader issue of antimicrobial resistance.

However, it is important to balance access restrictions with ensuring timely and appropriate access to antifungal medications for those who genuinely need them. Regulatory authorities should consider the potential impact on public health and work towards striking a balance that prevents misuse while ensuring patients with legitimate needs can obtain timely treatment. Additionally, comprehensive education and awareness campaigns should accompany such regulatory measures to inform the public about the rationale behind the restrictions and promote understanding of responsible medication use.

3.5.3. Restricting the Use of Antifungal Agents in Agriculture

Agricultural practices contribute significantly to the emergence of AFR, and regulatory measures are needed to address this issue [47]. Regulating the use of antifungal agents in agriculture and promoting sustainable farming practices can help minimize environmental exposure to these drugs [47]. Restricting the use of antifungal agents in agriculture is a critical strategy to address the emergence of AFR and safeguard both human and environmental health [47] [132].

It is critical to conduct thorough risk assessments to evaluate the impact of
antifungal use in agriculture on human health, animal health, and the environment. There is a need to develop risk management strategies based on these assessments to minimize potential negative effects [47]. Besides, countries need to establish surveillance systems to monitor the prevalence of AFR in agricultural settings. Moreover, regular monitoring can provide insights into the effectiveness of restriction measures and help identify emerging resistance patterns [47].

It is essential to provide education and training programs for farmers on sustainable farming practices and the potential risks associated with the overuse of antifungal agents [47]. This can enhance farmers’ understanding of antifungal use and resistance thereby leading to more responsible use of antifungals and helping prevent unnecessary applications [58]. Hence, much must be done to conduct public awareness campaigns to inform consumers about the potential risks associated with excessive use of antifungal agents in agriculture. This can influence consumer choices and create demand for sustainably produced agricultural products. In the agricultural sector, there is a need to encourage and promote alternative agricultural practices that reduce the reliance on antifungal agents [130]. This may include adopting crop rotation, using resistant crop varieties, and implementing integrated pest management strategies [40]. There is also a strong need to enforce regulations to restrict the use of certain antifungal agents in agriculture. This may involve setting limits on dosage, application frequency, or specific application methods. The implementation of regulatory frameworks can help ensure compliance with responsible use guidelines. Besides, there is a need to introduce systems that require farmers to obtain prescriptions or approvals from agricultural experts or authorities before using antifungal agents to ensure that these medicines are used only when necessary and per established guidelines [47].

Countries should invest in research and development to identify and promote alternative methods for controlling fungal infections in crops [43]. This includes developing biopesticides, resistant crop varieties, and sustainable agricultural practices that minimize the need for antifungal treatments. Other than that, it is critical to collaborate with international partners to share best practices, research findings, and regulatory approaches [165]. Global collaborations are essential to address the transboundary nature of AFR in agriculture [165]. Finally, there is a need to provide incentives, subsidies, or support programs for farmers who adopt sustainable and responsible agricultural practices that reduce the need for antifungal treatments.

By combining these strategies, it is possible to create a more sustainable and responsible approach to antifungal use in agriculture, thereby mitigating the risk of resistance development and promoting environmental and human health.

3.5.4. Heightened Infection Prevention and Control Measures in Healthcare Facilities to Prevent Fungal Infections and Address Antifungal Resistance

In healthcare settings, strict infection prevention and control (IPC) measures are
imperative to minimize the spread of fungal infections [190]. Some of the IPC includes promoting hygiene practices in both healthcare and community settings [191]. Additionally, regulatory measures, such as enforcing restrictions on the sale and use of antifungal medicines, can further contribute to the overall effort. IPC reduces the use of antibiotics and antifungal agents thereby preventing the emergence and spread of AMR, and specifically AFR [192].

Implementing heightened IPC measures in healthcare facilities is crucial for addressing AFR and preventing the spread of fungal infections [193]. It is important to ensure rigorous adherence to hand hygiene protocols among healthcare workers in clinical settings [191]. On top of that, proper handwashing with soap and water or using alcohol-based hand sanitizers can significantly reduce the transmission of fungal infections within healthcare settings [194]. Alongside this, there is a critical need to establish and promote AFS programs within healthcare facilities [80] [162]. These programs can optimize the use of antifungal medications, ensuring they are prescribed judiciously and by established guidelines [81]. There is also a need to provide ongoing education and training for healthcare workers on IPC measures specific to fungal infections [190]. This includes recognizing signs of fungal infections, proper use of antifungal medications, and adherence to established protocols [190] [191]. Ensure healthcare workers consistently use appropriate personal protective equipment (PPE), including masks, gloves, gowns, and eye protection, when dealing with patients with fungal infections [195]. This is essential for preventing direct contact and airborne transmission. Healthcare facilities should regularly review and update IPC protocols based on the latest scientific evidence and emerging trends in antifungal resistance [195]. Finally, healthcare must be flexible in adapting to new information is crucial for maintaining effective control measures [195].

It is critical to identify and isolate patients with confirmed or suspected fungal infections to prevent the spread of resistant strains. Implementing cohorts, where patients with similar infections are grouped, can further enhance infection control. Implement regular screening and surveillance for fungal infections, particularly in high-risk areas such as intensive care units. Early detection allows for timely intervention and prevents the spread of infections. Therefore, it is critical to educate patients and visitors about the importance of infection prevention measures, including hand hygiene and adherence to facility-specific protocols [196]. Consequently, informed individuals can actively participate in reducing the risk of infection transmission [191].

There is a need to implement stringent cleaning and disinfection protocols for surfaces and equipment in healthcare facilities [197]. However, fungi can persist on surfaces, and thorough cleaning is essential to minimize the risk of transmission. Hence, there is a need to emphasize and monitor aseptic techniques during medical procedures, especially those involving invasive devices or surgical interventions [198] [199]. Strict adherence to sterile procedures minimizes the risk of introducing fungal pathogens. Consequently, it is essential to implement envi-
Environmental monitoring programs to assess fungal contamination in healthcare settings. This can help identify areas at risk for fungal transmission and guide targeted infection control measures [93].

Finally, countries must foster collaboration and open communication between healthcare teams, infection control specialists, and microbiology laboratories [200] [201] [202]. Timely sharing of information allows for prompt responses to emerging fungal infections and potential resistance issues [200].

By integrating these heightened IPC measures into healthcare practices, facilities can contribute significantly to the containment of fungal infections and the prevention of AFR within healthcare settings.

3.5.5. International Collaborations in Addressing Antifungal Resistance

Addressing AMR, including AFR requires international collaborations [203]. International collaborations play a crucial role in addressing AFR, as fungal infections and the emergence of AFR are global health concerns that transcend national borders [201]. Countries must work together to share information, harmonize guidelines, implement surveillance programs, and collectively develop strategies to preserve the efficacy of existing antifungal agents. Additionally, international collaboration is crucial for addressing global challenges associated with AFR. Countries must share knowledge, expertise, and resources to develop and implement effective strategies on a global scale.

International collaborations must foster global information sharing and collaboration on surveillance data related to AFR [165]. In addition, establishing international databases allows countries to share information, monitor trends, and identify emerging resistance patterns. On top of that, we need to develop and promote harmonized international guidelines and standards for the diagnosis, treatment, and prevention of fungal infections. It is recommended that consistent approaches ensure that best practices are implemented globally, reducing the risk of AFR development. There is also a need to facilitate international research consortia to pool resources, expertise, and data for advancing research on antifungal resistance. Collaborative efforts can accelerate the development of new antifungal agents and improve treatment strategies.

Countries must support capacity-building initiatives in countries with limited resources to enhance their ability to address AFR effectively [92] [204] [205] [206]. This includes training healthcare professionals, improving laboratory capabilities, and strengthening surveillance systems [92]. Moreover, there is a need for coordinated efforts to implement and monitor AFS programs on an international scale. This involves optimizing the use of antifungal medications to minimize overuse and reduce the risk of resistance [92]. There is also a need to establish joint surveillance programs that involve multiple countries working together to monitor AFR, similar to what has been done under AMR [207] [208] [209] [210] [211]. This collaborative approach provides a more comprehensive understanding of the global landscape of resistance and enables coordinated responses. Over and above that, there is an urgent need to advocate for interna-
tional policies that prioritize the fight against AFR. Collaborative efforts in policy development can lead to unified strategies and commitments to address this global health challenge [40].

We need to facilitate the formation of cross-border research networks that bring together scientists, clinicians, and policymakers to collaborate on specific aspects of AMR, including AFR research [212]. This can include clinical trials, epidemiological studies, and surveillance initiatives. Additionally, there is a need to participate in and support global surveillance networks focused on AMR, including AFR. These networks, often facilitated by international health organizations, enable real-time information exchange and collaboration. Alongside this, there is a need to instigate collaborations on international public awareness campaigns to educate healthcare professionals, policymakers, and the public about the risks of AFR. A unified message can have a broader impact and promote collective action.

There is a need to promote regulatory harmonization to ensure consistent standards for the approval and monitoring of antifungal agents globally [40] [213], similar to reports regarding antibiotics [214] [215] [216]. Streamlining regulatory processes can facilitate timely access to effective treatments and promote responsible use [213]. On the other hand, countries must develop collaborative emergency response plans for fungal outbreaks that may have international implications. This includes sharing resources, and expertise, and coordinating efforts to contain and manage outbreaks effectively [213].

By fostering international collaborations across these various dimensions, the global community can strengthen its collective response to antifungal resistance, enhance surveillance capabilities, and promote effective strategies for prevention, diagnosis, and treatment on a global scale.

This review demonstrated that fungal infections and AFR affect humans, animals, and plants, and have an impact on the environment.

4. Conclusion

Antifungal resistance is a public health problem that already claimed many lives globally. This problem has been worsened by the inappropriate use of antifungal agents across humans, animals, and agriculture to treat or prevent fungal infections. Consequently, fungal infections have increased thereby causing a burden to the communities and the healthcare system. To address this problem, many strategies must be instigated and implemented across the One Health ecosystem. Additionally, AFS must be developed and implemented across all healthcare systems. Furthermore, recognizing AFR as a global public health problem necessitates a coordinated and multisectoral response. Efforts should focus on surveillance, research, education, policy development, and international cooperation to effectively combat the challenges posed by resistant fungal infections worldwide. Finally, there is a need to institute a multifaceted approach encompassing surveillance, education, research, regulatory measures, and international cooperation.
collaboration to effectively address AFR. Thus, by combining these strategies, stakeholders can work towards preserving the efficacy of existing antifungal agents and ensuring the continued success of fungal infection treatment.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References


tiffungal Azoles? Clinical Infectious Diseases, 62, 362-368. https://doi.org/10.1093/cid/civ885


https://doi.org/10.1128/CMR.12.4.501


https://doi.org/10.3390/encyclopedia2040118

https://doi.org/10.1038/s41579-022-00720-1

https://doi.org/10.1146/annurev-micro-030117-020345

https://doi.org/10.1007/s40265-022-01751-x

https://doi.org/10.3390/jof9050565


https://doi.org/10.1007/s10096-019-03713-w

https://doi.org/10.3390/antibiotics12111632

https://doi.org/10.3390/biom9100521

https://doi.org/10.3390/agriculture12020289


tem. *Antibiotics*, 14, Article 61. [https://doi.org/10.3390/IOC2023-14513](https://doi.org/10.3390/IOC2023-14513)


https://doi.org/10.1093/jac/dkaa428

https://doi.org/10.3389/fpubh.2023.1191036


https://doi.org/10.1186/s40545-023-00556-x

https://doi.org/10.1136/bmjgh-2020-003091

https://doi.org/10.3390/ph16111615