Resistance undermines treatment of fungal infections

To: the Minister for Medical Care, the Minister of Agriculture, Nature and Food Quality and the State Secretary of Infrastructure and Water Management
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Health Council of the Netherlands

contents

executive summary

Fungi are essential for the functioning of ecosystems. Additionally, they are used in the production of foodstuffs (bread, cheese, beer and wine), chemicals and medicinal products. We already know about over 100,000 species of fungi, but the actual number of species is somewhere in the millions. Around 300 species of fungi are known to cause infectious diseases in humans. These are mainly relatively harmless skin, nail and mucosal infections. However, when a fungus penetrates deeper into the body, this can result in a life-threatening invasive infection.

Fungal infections are treated with antifungal drugs (antimycotics). Long-term or repeated treatment can cause fungi to build up a resistance to these antimycotics, rendering them less capable, or completely incapable, of removing harmful fungi. Over the last few years, the use of fungicides in agriculture has led to cases of resistant fungi becoming more frequent. At the same time, we are encountering more new resistant species of fungi that could have severe health consequences. Consequently, antifungal resistance is becoming an ever-increasing problem.

In this advisory report, the committee on the Identification of Environmental and Health Issues looks into developments related to antifungal resistance and the consequences for public health. It also issues recommendations to the government on how to tackle this problem.

Antifungal resistance increases the disease burden from fungal infections

Relatively innocent skin, nail and mucosal infections caused by fungi are common: every year, at least 800,000 Dutch citizens use antimycotics to combat these infections on the advice of a physician. The number of people who buy these products at a pharmacy or supermarket is unknown. Around 250,000 people suffer from a more severe, chronic fungal infection.

Invasive fungal infections that are actually life-threatening are more rare, at around 3,000 cases per year. They occur in patients on hospital intensive care wards and patients who receive immunosuppressants over a longer time period in connection with cancer or a stem cell or bone marrow transplant. These infections are difficult to treat. Moreover, treatment of the underlying condition must sometimes be temporarily reduced, postponed or halted. The mortality rate is therefore high.

Antifungal resistance makes invasive infections even more deadly.
As a result of resistance, superficial skin and mucosal infections could take on more chronic and disabling forms, especially since the arsenal of antimycotics to which physicians have access is very limited. If one class of drug becomes ineffective due to resistance, few alternatives are available. In the event of resistance to multiple or all classes of drug, infections become virtually untreatable.

Resistance due to fungicides is increasing

Both in the Netherlands and worldwide, the number of species of fungi that are resistant to antimycotics is increasing, including yeasts (*Candida* genus) and skin fungi (*Trichophyton* genus). Moreover, resistance is also increasingly caused by non-medical uses of chemical fungicides.
The resistance to antimycotics of the fungus *Aspergillus fumigatus* is mostly due to its exposure to closely related fungicides used in agriculture and treated wood. Spores of resistant fungi can be found in piles of plant detritus, for example in the bulb-growing industry or in shredded waste wood. People may inhale spores of resistant fungi that spread through the air from these piles of detritus. This is not a problem for healthy people, but it may have serious consequences for people with a weakened immune system.

The committee has identified various developments that will likely increase the scope and severity of problems related to resistance.

Due to an ageing population, chronic illnesses and medical treatments that weaken the immune system, the group of people at high risk is growing continuously. Moreover, new, infectious and multiresistant species of fungi – such as the *Candida auris* yeast and the *Trichophyton indotineae* skin fungus, which have already caused considerable illness in other countries – have now appeared in the Netherlands as well. Globalisation and possibly climate change may have played a role in this.

Problems related to resistance are also increasing because the use of fungicides in agriculture is not being restricted sufficiently. Furthermore, fungicides re-enter the agricultural and food chains as a result of the recycling of polluted waste. New antimycotics risk losing their effectiveness very rapidly, because related substances for agricultural purposes are brought to market at the same time. So far, barely any effective policies have been introduced due to the limited interest in fungal infections and because no authority has been assigned the leading role of driving the approach to this issue, either nationally or internationally.

Advice: take action to tackle resistance

The committee concludes that fungal resistance to antimycotics is increasingly undermining the treatability of fungal infections in humans, forming a significant threat to public health. This problem is in many ways similar to that of antimicrobial resistance. The Netherlands has

already introduced a successful policy in this area and is a model for other countries to follow.

The committee believes that urgent action also needs to be taken in the field of antifungal resistance. With its advisory report the committee underlines the importance of attention being paid to fungi and their increasing resistance to antimycotics in the *National Action Plan on Antimicrobial Resistance 2024-2030* which is soon to be published and it makes several concrete recommendations that may help to limit the problem:

- Appoint a coordinating authority for the approach to the problem, with a leading role for the Ministry of Health, Welfare and Sports as the obvious choice.
- Combine, reinforce and better utilise existing expertise on fungal infections and antifungal resistance at the various institutes by setting up a Fungal Diseases Knowledge Platform. In doing so, promote a multidisciplinary approach to this issue. This has proven successful in combating antibiotic resistance.
- Expand existing surveillance programmes for antimicrobial resistance to include pathogenic fungi.
- Proactively tackle sources of increased antifungal resistance in the environment and identify sources that are still unknown.
- Within the European Union, and preferably even at the global level, push for a ban on using the active substances of new antimycotics (or closely related substances) in agricultural fungicides or for other broad uses, such as wood treatment. If this does not appear feasible, require manufacturers of new fungicides to prove in advance that their products will not have a negative impact on the effectiveness of antimycotics in humans.
- Reinforce the existing policy to reduce the use of fungicides and plant protection products in general. At the same time, encourage the sensible use of antimycotics, especially in primary care, and restrict the over-the-counter availability of specific antimycotics as necessary. This is in line with antibiotics policy, since these are also not freely available.
- Stimulate the development of additional medical interventions (such as vaccinations and immunotherapy) for the prevention or treatment of fungal infections. These can reduce the use of antimycotics and therefore limit the development of resistance.
- Task a newly Fungal Diseases Knowledge Platform with drawing up a national plan of action for fungal diseases, in which the aforementioned and any additional actions are elaborated further and the parties that need to be involved are identified.

01 introduction

1.1 Background

Fungi are neither plants nor animals. They form a distinct group of organisms. More than one hundred thousand species are known, but their actual number likely runs into the millions.[1-5] They are essential for the proper functioning of ecosystems.[6] Historically, humans have used them in the preparation of foodstuffs such as bread, cheese, beer and wine, and today they are also used for the large-scale industrial production of bulk chemicals and medicinal products.[7] However, fungi can also cause significant damage to materials, foodstuffs, stored agricultural products and crops in the field. They pose an ongoing threat to agricultural food production.[8] Humans have been attempting to prevent or limit the damage caused by fungi as much as possible through the widespread use of chemical crop protection agents and biocides.

Around 300 species of fungi are known to cause infectious diseases in humans.[3,9] Usually, these are relatively harmless but irritating or unsightly outward conditions of the nails, skin and mucous membranes, such as fungal nail infections, athlete's foot, ringworm, dandruff, oral thrush and vaginal infections.[10] Nevertheless, if these infections recur frequently or become chronic, they can significantly reduce a patient's quality of life. When the fungus penetrates deeper into the body, it can result in acute, life-threatening invasive infections. This occurs mainly as a complication in people who are in intensive care after surgery or an accident. People with HIV, as well as patients undergoing long-term treatment with immunosuppressive drugs for cancer or organ transplantation, are also more susceptible to invasive fungal infections. In recent years, such invasive infections have also been observed in patients with severe influenza or COVID-19.[11-14] In many cases, these infections involve fungi that are carried by everyone, either as part of the normal gut flora or because their spores are inhaled daily. A brief description of the most common fungal diseases can be found in the accompanying background document *Beschrijving van enkele schimmelziekten* (Description of some fungal diseases).

Each year, an estimated 2.5 million people worldwide die from the direct effects of invasive fungal infections.[15] In the Netherlands, around three thousand people develop a life-threatening fungal infection every year.[16] Depending on the fungal species, the timeliness of diagnosis and the underlying health condition, 35–90% of those affected die.[15] Additionally, a quarter of a million Dutch people suffer from chronic fungal conditions that can diminish their quality of life.[16] Each year, 0.8 to 0.9 million people in the Netherlands are prescribed[17] antifungal drugs (antimycotics) for infections of the skin, nails and mucous membranes, and an unknown number of people purchase treatments from pharmacies or supermarkets. Despite this, health authorities and medical professional organisations have, until recently, not regarded fungal infections as a serious public health threat, possibly because life-threatening invasive infections primarily affect people with pre-existing health conditions and are rarely,

if ever, transmissible. Compared to other infectious diseases, fungal infections have received limited attention.[10,18-22]

In recent years, fungi have increasingly developed antifungal resistance. Around the turn of the century, patients with severe *Aspergillus fumigatus* infections began to be identified that could not be adequately treated with azoles, the main class of antifungal drugs. The primary cause of this resistance was found to be the widespread use of closely related azole compounds in agriculture.[23-26] Recently, the issue of resistance appears to be spreading to other, partially newly discovered, easily transmissible pathogenic fungal species and other classes of antimycotics. This is particularly concerning because the arsenal of available antimycotics is very limited. In response, the WHO published its Fungal Priority Pathogens List at the end of 2022, which includes the 19 most medically significant fungal species.[19,27] The problem of antifungal resistance increasingly resembles the issue of bacterial resistance to antibiotics.

1.2 Committee and objective

This report has been prepared by the Health Council's permanent committee on the Identification of Environmental and Health Issues. The committee's task is to monitor issues related to the living environment and health, and to bring relevant developments to the attention of the government and parliament. In this report, the committee addresses the issue of antifungal resistance and its medical consequences. Based on the current state of scientific knowledge, it outlines the severity and scale of the problem, its underlying causes and the gaps in knowledge. It also looks ahead to potential future developments and makes recommendations to the government, as well as to producers and users of antifungal agents, on how to address knowledge gaps and mitigate the problem. For this specific topic, the committee was temporarily expanded with three experts in the field of fungal diseases and resistance. The composition of the committee is listed at the end of this report.

1.3 Methodology

The scientific literature on fungal diseases and antifungal resistance is voluminous. Therefore, the committee primarily relied on recent review articles from authoritative scientific journals[3,9,18,28-35] and reports from respected national, foreign and international institutions.[36-39] Where necessary, the committee also reviewed publications on the results of individual studies. Additionally, the committee largely confined its considerations to three (groups of) fungal species: *Aspergillus fumigatus* and species of the genera *Candida* and *Trichophyton*. These cause a relatively high number of serious fungal infections in the Netherlands and elsewhere in the world and, in their diversity, can serve as models for a much broader spectrum of fungi and their resistance development. The key terms used by the committee are briefly explained in the accompanying glossary. Finally, the committee draws parallels with the

issue of antibiotic resistance and seeks to learn from the experiences gained with measures in that area. Where relevant, the committee refers to previous reports by the Health Council.

1.4 Reading guide

In Chapter 2, the committee first briefly describes the limited arsenal of drugs available to physicians for treating fungal infections. It then explains how fungi can develop resistance to these drugs, the conditions that facilitate this development and the global scale of the resistance problem. Chapter 3 discusses the significant medical consequences. In Chapter 4, the committee outlines the prospects before drawing its conclusions and offering recommendations to the government in the final chapter, aimed at curbing the resistance issue.

Terminology

- Antimycotic (plural: antimycotics): a drug used for the treatment or prevention of fungal infections in humans and animals.
- Biocide: a chemical agent used for purposes such as controlling pests in and around homes and barns, for disinfection, or for the preservation of materials like wood, textiles and paint.
- Fungicide: a crop protection agent or biocide used to treat fungal infections or prevent spoilage caused by fungi.
- Crop protection agent: a chemical agent used to combat diseases and pests in crops and to protect the harvest. Herbicide: a crop protection agent used to control weeds in fields and on paved areas.
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- Isolate (in fungi): a fungus that has been isolated (i.e. extracted) from a sample obtained from a patient (clinical isolate) or from the environment (environmental isolate) and then cultured in pure form for identification and further research.
- Cross-resistance (in fungi): possession or acquisition of a single resistance mechanism that makes the fungus simultaneously resistant to multiple, usually closely related (i.e. with the same mechanism of action) antimycotics or fungicides.
- Multi-resistance (in fungi): resistance to multiple classes of antimycotics or fungicides.
- One Health: an approach to designing and implementing programmes, policies, legislation, or research, in which experts in human health, veterinary health and ecosystem health share information and collaborate to promote public health. The principle is that the health of people, animals and the environment are closely interlinked.
- Pan-resistance (in fungi): resistance to all available classes of antimycotics or fungicides.
- Resistance (in fungi): a reduced sensitivity or complete insensitivity of a fungus to an antimycotic or fungicide, rendering the fungus inadequately or not at all affected by the treatment. Resistance can be acquired, meaning it results from a recent genetic change in the fungus, or intrinsic, meaning the fungus is naturally insensitive to the agent.
- Strain (in fungi): a specific genetic variant of a fungal species.

02
antimycotics and the development of resistance

Fungi can develop resistance during the treatment of an infection with antimycotics, particularly if the drugs are administered over a prolonged period or repeatedly. However, resistance is increasingly arising from the presence of fungicides in the environment due to their use in agriculture or for the preservation of wood, textiles and paint. As a result, many dangerous fungal species have developed resistant, and sometimes multi-resistant, strains that spread rapidly across the globe via the air, migrating wildlife, travellers and trade routes.

2.1 Medications for fungal infections

Physicians have a limited arsenal of drugs, known as antimycotics, to treat fungal infections in humans. There are four main classes of antimycotics, along with a few standalone drugs (see the background document entitled *Chemical fungal agents in various sectors and extent of use*). Each class consists of several chemically related drugs that work in the same way. All classes of antimycotics either damage fungal cell membranes or cell walls, or prevent the formation of new cells, thus stopping fungal growth. The different classes achieve this in distinct ways. Having multiple classes available is crucial: if a fungus becomes resistant – i.e. less sensitive or completely unresponsive – to one medicine in a class, the other drugs in the same class are usually also less or no longer effective. In such cases, physicians must switch to another class of medicine to successfully treat the patient.

Only three classes of antimycotics are effective against the most common severe invasive fungal infections: azoles, polyenes (amphotericin B) and echinocandins.[40] Azoles are the preferred treatment for invasive Aspergillus infections (aspergillosis). They can be administered both intravenously (via the bloodstream) and orally, are inexpensive and have relatively few side effects. The other two classes must be administered intravenously. Echinocandins are costly and polyenes (amphotericin B) have relatively many side effects.[41] Azoles are also used to treat *Candida* vaginitis and fungal infections of the skin and nails. For skin and nail infections, allylamines (e.g. terbinafine) can also be used. Both groups of drugs can be administered orally or topically. Other polyenes, apart from amphotericin B, are used to treat conditions such as eye infections (natamycin, though not in the Netherlands), oral thrush and *Candida* vaginitis (nystatin), and are applied locally.

The number of available classes of antimycotics for treating fungal infections is small compared to the number of antibiotic classes used to combat bacterial infections. For example, there are six different classes of antibiotics available to treat methicillin-resistant *Staphylococcus aureus* (MRSA).[40] The limited availability of antimycotics stems from the fact that fungi, at the cellular level, are more closely related to humans than bacteria are. This makes it difficult to develop antifungal drugs that have few or no harmful side effects on humans. Moreover, manufacturers face challenges in recouping the significant investment needed to develop

these drugs. This issue is likely more pronounced for antimycotics than for antibiotics. In the case of antimycotics, there is a higher chance that a drug might prove too toxic for humans during the development process. The costs incurred for drugs that fail prematurely must be recouped from the few that make it to market. Additionally, the market for antimycotics is smaller.

2.2 The development of resistance

Nearly all antimycotics damage the fungal cell membrane or cell wall, or hinder the production of essential building blocks needed to form new cell membranes or walls. This stops the growth of the fungus. Fungi can become less sensitive to antimycotics in various ways.[42] They can activate transport proteins (efflux pumps) in the cell membrane, which hasten the removal of antimycotics from the cell. Additionally, fungi can form a protective slime layer (biofilm) that makes it harder for antimycotics to come into contact with or penetrate the cell. In both cases, a smaller portion of the administered antimycotic reaches its intended targets, usually enzymes involved in forming crucial building blocks for the cell membrane or wall. Antimycotics typically work by binding to these enzymes and rendering them inactive.

Fungi can also become less sensitive through changes in the enzymes themselves.[42] Due to mutations in the relevant genes, the enzymes may alter slightly in shape, preventing the antimycotics from binding effectively. Any reduction in enzyme effectiveness due to this change in shape can be offset by increased enzyme production, driven by additional genetic changes. Efflux pump activation, biofilm formation and alterations in enzymes also play a significant role in the development of antibiotic resistance in bacteria.[43,44]

The genetic changes underlying these resistance mechanisms arise spontaneously and randomly in living fungal populations. However, some fungal species naturally possess such mechanisms. In such cases, this is referred to as intrinsic rather than acquired resistance. These resistance mechanisms give fungi that possess them a competitive advantage over those that do not. This occurs even at very low concentrations of antimycotics, where the fungi may still experience some negative effects but can continue to grow. Gradually, fungi with these mechanisms outcompete their more sensitive counterparts, making up an increasing share of the population. This process is known as selection.

Areas with low concentrations of antimycotics inevitably develop with each use. Some parts of the body are difficult for the medicine to penetrate. In other areas, breakdown and transport processes result in low concentrations. This creates opportunities for less sensitive fungi to be selected. For certain fungal species, it has been shown that sexual reproduction can result in offspring inheriting combined resistance mechanisms from both parents.[45] Further genetic changes can lead to

the accumulation of additional resistance mechanisms, making the fungal population progressively less sensitive. Exposure to multiple classes of antimycotics can cause fungi to become resistant to several, or in rare cases, all classes. This leads to the emergence of multi-resistant and pan-resistant strains.

2.3 Resistance development during medical use

The development of antifungal resistance during patient treatment is known, though relatively rare. The risk is highest when treatments need to be administered for extended periods or repeatedly. Azoles, in particular, are prone to resistance development. During the treatment of chronic fungal diseases, such as chronic aspergillosis, thrush in HIV patients and recurrent vulvovaginitis, fungi like *Aspergillus fumigatus* and *Candida albicans* can develop resistance.[25,46-49] This also occurs when patients with significantly weakened immune systems (such as those with HIV, cancer, or recipients of stem cell or organ transplants) are given azoles for extended periods as a preventive measure (prophylaxis) against fungal infections.[46,50] In addition, prolonged azole treatment can lead to the selection of rarer fungal species that are either intrinsically resistant or can easily acquire resistance, such as *Aspergillus calidoustus*[51] or species like *Candida krusei*, *Candida glabrata*, *Candida tropicalis* and *Candida parapsilosis*.[30,39,50,52-55]

Resistance can also develop in pathogenic fungi during prolonged administration of echinocandins.[56-58] However, this occurs less frequently with polyenes.[41,59,60] For example, *Candida auris*, which was first discovered in Japan in 2009 and is now causing outbreaks of infections in hospitals worldwide, has been found to develop resistance relatively easily to the polyene compound amphotericin B during treatment.[61]

Skin fungi such as *Trichophyton rubrum* can become resistant to allylamines, particularly terbinafine.[62-64] In India, *T. rubrum*, the main cause of skin infections, has already been displaced by a recently discovered terbinafine-resistant species, *Trichophyton indotineae*, likely due to the widespread use of over-the-counter combination creams containing corticosteroids, antimycotics and antibiotics.[65,66] So far, the personal use of over-the-counter antimycotics for superficial fungal infections in Western countries has not led to significant resistance problems.[67,68]

2.4 Resistance development in the environment

Antimycotic resistance can also develop outside the medical domain. This is particularly true for azoles, as chemically similar compounds are widely used as fungicides in agriculture and for the preservation of wood, textiles and paint (see the related background document).[69] As a result, azoles are ubiquitous in the environment. By contrast, echinocandins and polyenes are almost exclusively used in medical treatments.

The only polyene compound used outside of medicine is natamycin, which serves as a preservative in the food industry. However, antimycotics

from both human and veterinary medicine also enter the environment in significant amounts through wastewater treatment plants, sewer overflows and manure spreading, as well as, in some countries, through the spreading of sludge from water treatment plants.[70] This section provides summaries for selected fungal species of what is known about the impact of environmental exposure on resistance development, where resistance primarily develops (hot spots), and the transmission routes through which humans and animals may become infected with resistant fungi.

Aspergillus fumigatus

In the Netherlands, more than half of all patients with severe azole-resistant *A. fumigatus* infections have never been treated with antimycotics.[71] The fungi isolated from these patients possess a distinctive combination of genetic mutations, which are also commonly found in environmental strains living in areas with abundant dead plant material (the natural habitat of this species). These areas are often contaminated with azole-containing fungicides used in agriculture. While *A. fumigatus* itself is not a plant pathogen and is not directly targeted by these fungicide sprays, it is exposed to them, leading to the selection of strains that are resistant to fungicides. This results in cross-resistance to the chemically related medical azoles. Often, fungi isolated from patients also carry resistance genes against other fungicides that are used exclusively in agriculture.[72-75] This suggests that patients become infected with fungi that have already developed resistance in their natural environments.[24,71,76,77] These infections occur when patients inhale resistant *A. fumigatus* spores, which are ubiquitous in the air and can germinate in individuals with weakened immune systems.

In the Netherlands, initial investigations identified piles of plant waste from bulb cultivation, other plant material waste and shredded wood treated with fungicides as key sources of resistant spores.[78] In bulb waste, resistant strains were found even in the presence of extremely low levels of azoles (80 µg of prochloraz per kg of plant material).[37] Subsequent studies revealed that waste piles from onion, strawberry and potato farming also serve as major sources of resistant spores.[79] There are likely to be additional sources that have not yet been identified. Waste from grain and fruit cultivation, maize silage and household green waste are not considered sources of resistant spores in the Netherlands. In the United Kingdom, soils in private gardens enriched with homemade or store-bought compost have been identified as a source of resistant spores.[80] It is evident that resistance arises not so much during cultivation but afterward, during the processing of plant waste from fungicide-treated crops.[81]

Candida species

For *Candida* species, the role of the environment in the development of resistance is harder to determine.[82] No distinctive genetic signature associated with environmental resistance development has been

identified. Additionally, resistant isolates from untreated patients can often be explained by transmission between patients. Nevertheless, the role of the environment in Candida species seems more significant than previously thought.[39] Laboratory experiments show that agricultural azoles can potentially induce cross-resistance to medical azoles in *C. glabrata* and *C. parapsilosis*.[83,84] Resistant and non-resistant strains of *Candida* species, including *C. auris*, are found in various soils and surface waters.[85-90] Evidence of environmental resistance development appears strongest for *C. tropicalis*.[28] Azole-resistant isolates of this yeast from both the environment and patients in Asia and South America are genetically similar.[85,91-95] Moreover, a significant portion of patients with resistant *C. tropicalis* infections had not been treated with azoles, and there were no indications of patient-to-patient transmission.[28,91,96-99]

Wild and domestic animals may also act as reservoirs and spreaders of resistance.[82,92,100] *Candida* species are a normal part of the natural microbiome of animals' skin and mucous membranes. There are increasing reports of azole-resistant *Candida* species in livestock and wild animals, even though azoles are rarely (in veterinary practice) or never (in wild animals) used as veterinary drugs.[82] Animals may acquire resistant *Candida* from the environment, or they may be exposed to azoles in their feed or surroundings, promoting resistance development in their microbiomes. This scenario is also known from antibiotic-resistant bacteria. Animal feed and manure from livestock are known to contain traces of azoles.[101] Whether the resistance mechanisms in animal isolates are the same as in human clinical isolates is yet to be investigated.[82]

Resistant *Candida* species are also increasingly being found in humans. It remains unclear whether this rise in resistance in clinical settings is solely due to the medical use of antimycotics or if environmental exposure to azoles plays a role.[82] Humans are exposed to azoles and other fungicides through sprayed food, work and proximity to treated agricultural fields.[102-104] Some experts are concerned that levels of exposure considered toxicologically safe through food might promote resistance development in *Candida* species within the human microbiome.[105,106] Similar concerns have been raised about the use of natamycin as a preservative in yogurt and beverages.[107-110] Furthermore, it has been suggested that fruits treated with fungicides post-harvest for preservation may play a role in the selection and transmission of resistant *Candida* species, including *C. tropicalis*, *C. parapsilosis*, and *C. auris*, to humans.[111-115]

Trichophyton species

The skin fungus *Trichophyton rubrum* originated as a soil inhabitant, feeding on the breakdown of keratin – a tough protein abundant in animal remains such as skin, nails, hair and feathers. Over time, strains that could best break down keratin at temperatures of 30-40°C and slightly alkaline pH levels – conditions similar to those found in the human skin's

outer layer – evolved from soil dwellers to skin residents. The recently discovered species *T. indotineae* has likely made a similar transition. Closely related fungi have been found in soils in India[65], and the extensive use of over-the-counter antifungal creams there may have contributed to this. These creams often contain, in addition to antifungals, potent corticosteroids and antibiotics, which suppress the host's immune system and alter the skin's microbiome, two natural defences against such fungal infections. It is unclear whether *T. indotineae* acquired resistance to azoles and terbinafine after its transition from soil to skin or earlier through contact with agricultural fungicides or medicinal residues in the environment.

In conclusion, resistance to azoles in *A. fumigatus* is primarily the result of the use of azole-containing fungicides in agriculture, while the significance of environmental exposure to antifungals for *Candida* and *Trichophyton* species remains unclear. For all three fungal species, further research is needed to determine the relevant locations and transmission routes for resistance development and human infection.

2.5 The scope of the resistance problem

Some experts suggest that resistance to antifungals in fungi develops more slowly than resistance to antibiotics in bacteria.[43,44] This is because fungi, unlike bacteria, have limited or no ability to exchange DNA, including resistance genes, across species. Therefore, resistance must develop anew in each fungal species.[31] However, this does not prevent resistant fungi from spreading rapidly across the world through airborne spores, traveling humans or migrating wild animals, or via trade and transport of livestock, agricultural products, compost and other goods.[116-121]

Aspergillus fumigatus

Azole resistance is now observed worldwide in clinical isolates of *A. fumigatus*, often exhibiting the characteristic genetic mutations seen in fungi that developed resistance in the environment. The percentage of resistant isolates generally ranges from a few percent, but in the Netherlands and the UK, it is between 10-15%.[26,122,123] In environmental hot spots, such as plant waste piles in Dutch bulb cultivation and soil in greenhouses in China, resistance levels can reach as high as 50-80%.[37,124] Resistance to echinocandins and polyenes in *A. fumigatus* is much rarer.[123,125] Nevertheless, resistance to amphotericin B has gradually increased in recent years[126], posing a growing concern in healthcare, particularly in Brazil[127,128] and Canada[129,130].

Research conducted at Radboud University Medical Center (Radboudumc) in Nijmegen shows that azole resistance in clinical isolates of *A. fumigatus* only appeared after 1999. Older isolates did not exhibit any resistance (see Figure 1).[131]

Resistance of *A. fumigatus* to azoles has been increasing since 2000

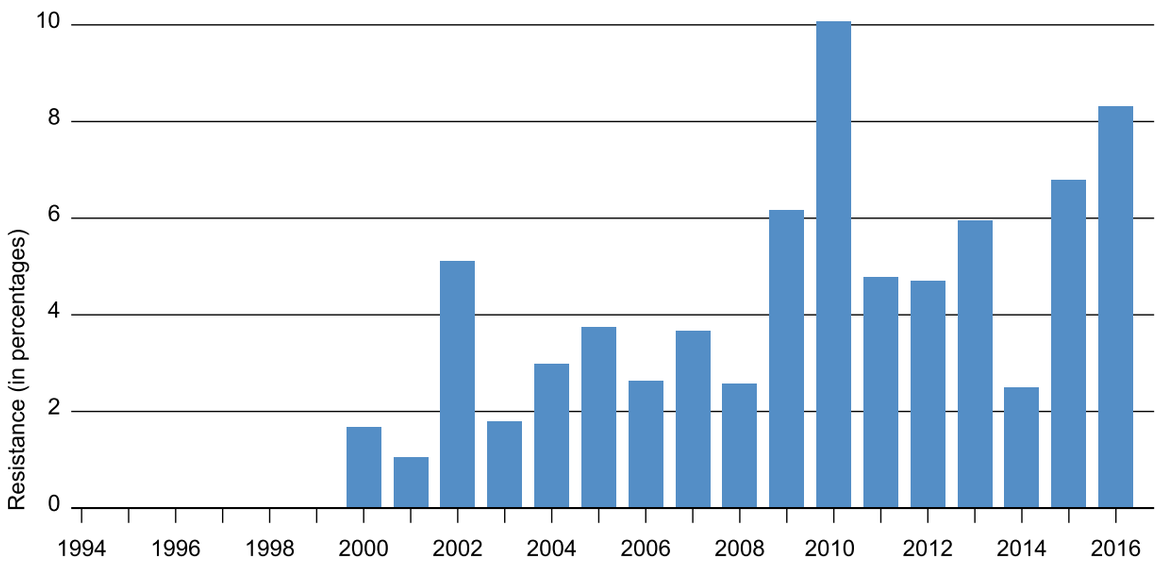

Figure 1 The percentage of cultured clinical isolates of *A. fumigatus* at Radboudumc that are resistant to azoles over the period from 1994 until 2016. Resistant isolates were first detected in 2000.[131]

Since 2007, resistance development in *A. fumigatus* has been monitored more widely in the Netherlands. Since 2013, it has been tracked by the Dutch Working Party on Antibiotic Policy (*Stichting Werkgroep Antibioticabeleid*, SWAB). Clinical isolates from patients with Aspergillus infections at five university medical centres (UMCs) and five other teaching hospitals are tested for their sensitivity to medical azoles.[132] In 2022, the frequency of triazole resistance averaged 7.7%, with higher rates in UMCs (10.6%) and lower rates in the other teaching hospitals (4.8%). After an initial sharp rise to 14.7% in 2018, the data from all hospitals together show a slight downward trend over the last five years, though this is not consistently observed in every hospital. In 82.5% of cases, the fungus had acquired its resistance in the environment, as indicated by its characteristic genetic signature. There are no clear, consistent regional differences.

Candida species

Resistance to antifungals is also an increasing problem with *Candida* species[30,55,82,133] A progressive shift is occurring in the species spectrum, with species that easily acquire resistance, such as *C. glabrata* and *C. parapsilosis*, accounting for a growing share of the disease burden at the expense of *C. albicans*.[39,55,134] However, there are significant differences between geographic regions and among the various species. The biggest challenges arise from *C. glabrata's* resistance to echinocandins and *C. tropicalis*' resistance to azoles. The latter is particularly prevalent in Asia and the Pacific region, with resistance rates to fluconazole in clinical isolates reaching over 40%, much higher than in other parts of the world. In China, resistance of clinical *C. tropicalis* isolates to azoles has sharply increased over the past decade (see Figure 2).[135]

Resistance of *Candida tropicalis* to medical azoles is increasing in China

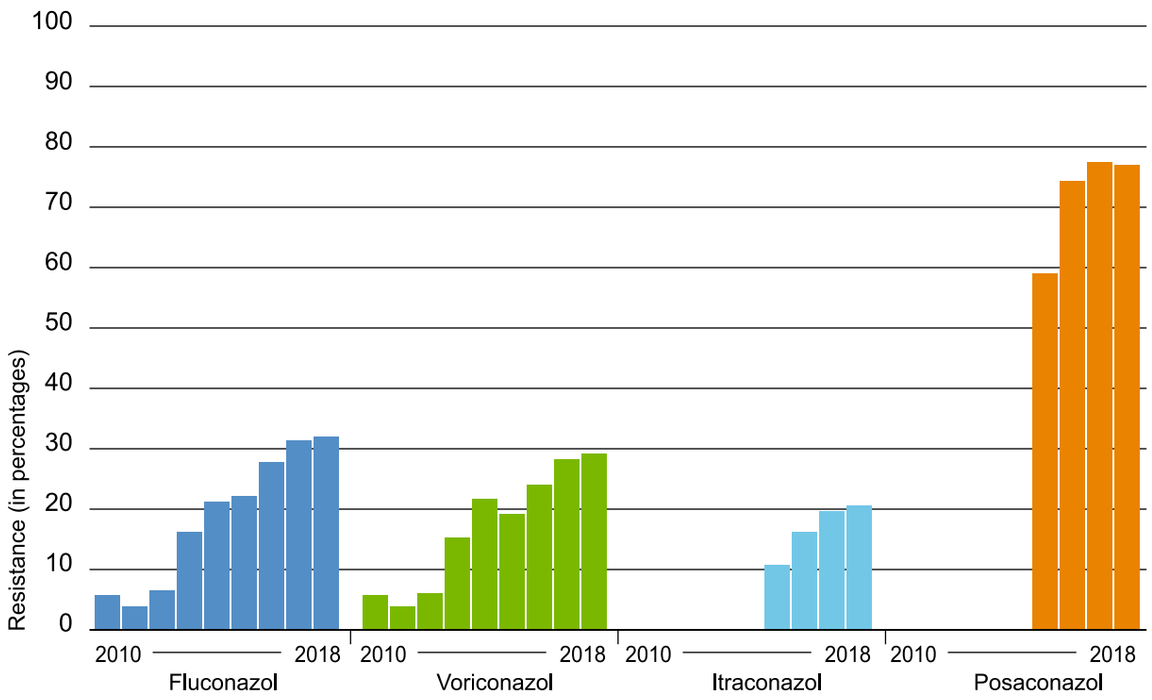

Figure 2 Trend in resistance of *C. tropicalis* to various medical azoles in China during the period 2010-2018. No data were available for itraconazole and posaconazole in the first five years.[135]

Fluconazole resistance in *C. parapsilosis* is most common in Europe, with a rate of 15.1%. In comparison, resistance in *C. albicans* in the same region is much lower, at only 0.4%.[82] Fluconazole-resistant *C. parapsilosis* has caused hospital outbreaks in countries such as Germany, France, Greece, Italy, Mexico, Spain, Turkey and South Africa.[30,136-140] Additionally, increasing cross-resistance to echinocandins is being observed in this species.[18,141,142]

A major new challenge is *C. auris*, first discovered in Japan in 2009 from a patient's ear infection, now causing outbreaks of invasive candidiasis in hospitals across more than 50 countries on five continents.[143] In Europe, outbreaks have occurred in the UK, Italy and Spain.[144,145] Over 90% of all isolates of *C. auris* are resistant to fluconazole, 30–50% to amphotericin B and around 5% to echinocandins.[20,61] Notably, *C. auris* is the only yeast species where resistance has been found across all classes of antifungal agents, with resistance rates of up to 4% in certain subpopulations.[143] While no outbreaks have occurred in the Netherlands, *C. auris* has been identified at least 20 times in patients transferred to Dutch hospitals from abroad.[146]

Trichophyton species

T. rubrum is a common cause of tinea corporis (ringworm). *T. rubrum* first showed terbinafine resistance in North America in 2003. Cases of terbinafine-resistant *T. rubrum* have also been reported in the Netherlands, although the frequency is unknown due to the lack of surveillance or epidemiological research.[148] Before 2018, very few cases were documented. Other European countries have reported terbinafine and azole resistance in *T. rubrum*.[149-152] Recently there seems to be an increase in Denmark (see Figure 3).[63]

Resistance of *Trichophyton* to terbinafine is increasing in Denmark

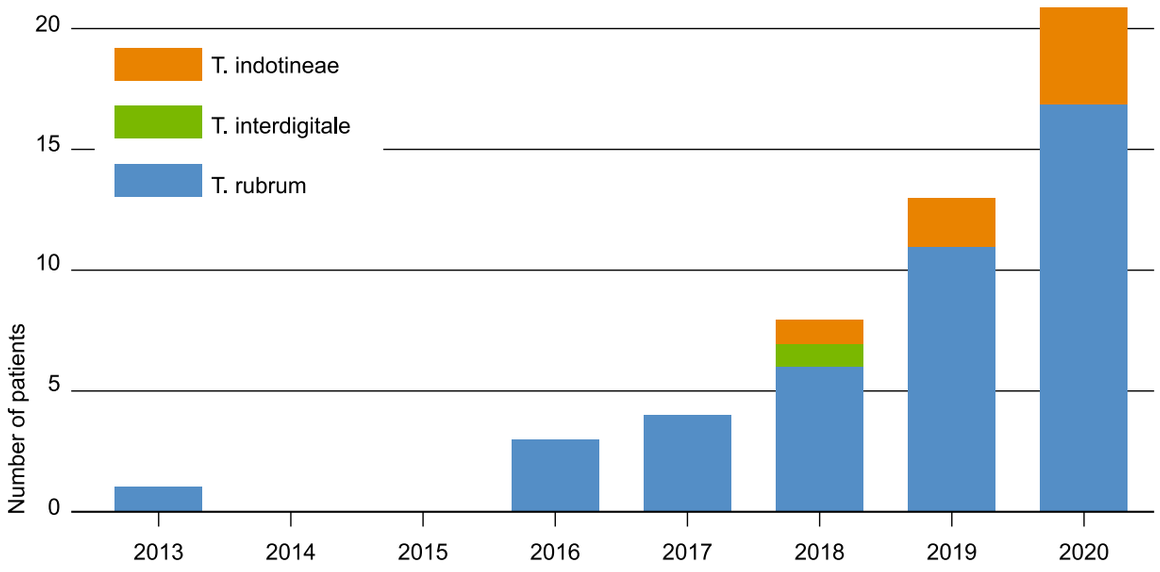

Figure 3 The annual number of Danish patients with a *Trichophyton* isolate resistant to terbinafine from 2013 to 2020.[63]

Another recently discovered skin fungus, *T. indotineae*, has rapidly spread from parts of Asia to the rest of the world.[120,153-155] In India, where serious skin infections have reached epidemic levels, 17–70% of isolates are resistant to terbinafine, and some are also resistant to azoles.[119,154,155] This species has been found in the United States[156,157] and several European countries, including Germany[119], France[151,158], Denmark[63] and the Netherlands[66,159].

For all the mentioned fungal species, the observed increase in resistance cannot solely be attributed to heightened awareness or more sensitive analytical techniques. Screening of large sets of isolates collected over many years shows a real increase in resistance.[63,131,135,160-163]

03
medical implications of antifungal resistance

Fungal infections are often difficult to treat. Severe invasive fungal infections become even deadlier due to resistance, and relatively mild superficial infections can become debilitating. This is mainly because the arsenal of antifungals available to physicians is very limited. In the event of resistance to multiple or all classes of drug, infections become virtually untreatable.

3.1 Invasive fungal infections

Treating fungal infections is often challenging. In cases of severe invasive infections, the risk of death is substantial. There are several reasons for this. First, patients with severe fungal infections almost always have other serious underlying conditions or severely weakened immune systems, which greatly complicates successful treatment of the infection. Additionally, physicians often do not immediately consider a pathogenic fungus as the cause of the symptoms. Furthermore, the isolation, culture and diagnosis of fungi are complicated due to a lack of knowledge and suitable identification tools[25,164,165], while the treatment needed varies greatly depending on the fungal species.[166] Specialised knowledge is required to identify relevant immune deficiencies and, where possible, to initiate targeted immunotherapy. Many antifungal agents are also known to cause side effects or interact with other drugs, requiring pharmacological expertise for optimal treatment selection and management of potential interactions.

Fungal resistance is generally detected late.[25,164] For patients with invasive aspergillosis, resistance testing is often not carried out, as there is no positive culture and therefore no available isolate. In patients who have never been treated with azoles, there are no clinical risk factors suggesting resistance. Most hospitals do not conduct their own resistance tests for fungi but send samples to specialised laboratories. Available commercial genetic tests for use in hospitals have limited sensitivity and do not detect all known resistance mutations.[25,164] Moreover, mixed infections involving both azole-sensitive and azole-resistant spores can occur. In some cases, it can take around ten days before the correct treatment is initiated.[25] For patients with invasive aspergillosis, this delay is associated with a 20–30% lower survival rate compared to those who receive the correct treatment immediately.[167-169] Current guidelines therefore recommend that, in areas where the resistance rate in clinical isolates is 10% or higher, invasive aspergillosis should be treated from the outset with a combination therapy of azoles and echinocandins or amphotericin B, with de-escalation to azole monotherapy once resistance testing results indicate this is appropriate.[164,170] This approach is expected to improve the survival chances of patients with azole-resistant invasive infections. Nevertheless, more than half of the patients with azole-resistant invasive aspergillosis still die. Some forms of invasive aspergillosis, such as voriconazole-resistant cerebral aspergillosis, are untreatable.[171]

A growing proportion of severe invasive *Candida* infections are caused by species other than *C. albicans*, such as *C. glabrata* and *C. parapsilosis*. Due in part to the relatively high incidence of fluconazole resistance in these species, treatment with echinocandins is the standard approach. However, the increasing resistance to echinocandins, especially in *C. glabrata*, is concerning, as this leaves amphotericin B as the only remaining treatment option. In *C. auris*, which is still relatively rare in much of Europe, 90% of cases are resistant to fluconazole and 30% are also resistant to amphotericin B, making monotherapy with echinocandins the preferred choice. However, resistance to this class can easily develop during treatment. A small percentage of isolates are pan-resistant and untreatable. Of those patients with *C. auris* in the bloodstream, 30–70% die.[143,145] *C. auris* and *C. parapsilosis* are also easily transmissible through direct contact and can survive for extended periods on or in the bodies of patients and on surfaces in hospitals. These characteristics make both species feared causes of hospital outbreaks.[140,142,143,172] The rise of these often multi-resistant species in Europe has significant implications for hospital prevention policies, similar to those associated with the MRSA bacterium.[143]

Research has shown that while fewer people in the Netherlands die from invasive fungal infections than from bacterial infections, the impact of resistance on mortality is significantly greater for invasive fungal infections. This is likely because physicians have sufficient alternative treatment options for bacterial infections, but not for fungal infections.[164]

In cases of chronic pulmonary aspergillosis, if azole resistance is present, the physician must switch to treatment with echinocandins or amphotericin B. Given that these agents can only be administered intravenously, this is an unattractive (but often unavoidable) alternative, particularly since patients are treated at home and the treatment duration typically ranges from 6 to 12 months.

The conclusion is that resistance in pathogenic fungi forces patients with severe and life-threatening fungal infections to be treated with combinations of agents or with alternative agents that are essentially second or third-choice options. These treatments are not only more expensive but usually also have more and more severe side effects.[164] This is especially problematic as these patients are often already severely weakened by an underlying illness, which contributes to the higher mortality rates in cases of resistance. For some fungal infections in cancer patients, treatment of the underlying disease, such as chemotherapy, must be reduced, delayed or stopped, reducing the chances of a successful cancer treatment. In the long term, the replacement of azoles with echinocandins and amphotericin B fosters the development of resistance to these agents.

3.2 Superficial fungal infections

Resistance can also have significant consequences for superficial fungal infections. The increasing azole resistance in *C. albicans* and the shift towards other, more resistant species such as *C. glabrata* and *C. krusei* as causes of recurrent vulvovaginal *Candida* infections often mean that effective treatment is no longer possible.[30,48,49] The growing resistance in *T. rubrum*, and particularly *T. indotineae*, to terbinafine complicates the treatment of severe ringworm infections.[120,153-155,173] Oral administration of itraconazole, preferably in combination with topical azole treatment, is then the preferred approach. Given the high contagion rate, simultaneous treatment of all affected family members is crucial.[173] However, this treatment is expensive.[120] Moreover, resistance to azoles in *Trichophyton* species is also increasing, leaving few treatment options available.[120] Recurrent vulvovaginitis and persistent severe skin infections have a highly disabling effect on patients and significantly impact their quality of life.[49,174]

04 outlook

The committee expects the issue of antifungal resistance to increase in both severity and scale over the coming years. The at-risk groups for fungal infections are becoming larger, and new resistant pathogenic fungal species are being discovered continuously. The use of fungicides is increasing, and recycling causes fungicides and antifungal agents to be reintroduced into agricultural production and food chains. New antifungal agents are at risk of becoming less effective even before they enter the market, due to the concurrent introduction of new fungicides with the same mechanisms of action in agriculture. So far, effective policies to address this issue are lacking.

4.1 The scale of at-risk groups

The number of serious fungal infections in humans is increasing worldwide, and this trend is expected to continue in the coming decades. This is due to the fact that the groups at increased risk of serious fungal infections are growing, driven by an ageing population, the rise in diseases that make people more susceptible to fungal infections (such as cancer, diabetes and infections caused by the influenza virus and SARS-CoV2), and the expanding possibilities in medicine for cancer treatment and organ transplants. This may also apply to less severe infections. Data on the use of antifungal agents in Dutch nursing homes indicate that the percentage of residents using antifungals increased from 2.3% to 6.0% between 2017 and 2021. The increase mainly concerned the use of ketoconazole, a treatment for fungal infections of the skin. Further research is required to determine whether the increase is due to a change in the susceptibility of the resident population or other factors, such as changes in prescribing behaviour. The use of antibiotics rose only slightly during the same period.[175]

4.2 The fungal kingdom as a reservoir for new pathogens

Fungi are also referred to as the ‘Hidden Kingdom’.[176] Less than 10% of the estimated millions of existing fungal species have been described. The greatly improved genetic analysis techniques are leading to rapid discoveries and make it possible to distinguish new species from previously known ones. Currently, much attention from scientists and health authorities is focused on new pathogenic fungi, such as *C. auris* and *T. indotineae*, and the associated resistance issues. However, in Asia, new pathogenic fungi have already been discovered: *C. vulturna*[177] and *C. khanbhai*[178], two close relatives of *C. auris*, which, like *C. auris*, are multi-resistant pathogens. The former recently caused an outbreak in China.[179] This demonstrates that the fungal kingdom is an inexhaustible reservoir of new pathogens, and it is now known that they can spread rapidly across the globe due to globalisation.

Experts expect that climate change will contribute to an increase in the number of fungal infections in humans.[9,180-185] The number of extremely hot days has risen sharply, providing selection events for heat tolerance that may enable environmental fungal species to evolve into new pathogens

for humans. Some experts see this as a plausible explanation for the emergence of *C. auris*.[180,186-189] Other fungi are expected to follow. Some experts challenge these claims, however, considering the temperature rise too modest and pointing out that many soil fungi, despite their ability to grow at 37°C, are not opportunistic pathogens for humans.[185] They consider other climate change-related factors to be more important, such as altered rainfall and wind patterns, desertification and dust storms that result in the expansion of the geographic distribution of fungal species and enhance the airborne spread of spores. Other relevant factors include refugee migration flows due to climate change and the direct and indirect effects of climate change on the immune system.[190]

4.3 Use of fungicides in agriculture and as biocides

The use of fungicides and crop protection agents in general is rising worldwide, and this trend is expected to continue in the coming years.[191,192] In the Netherlands, usage has remained relatively stable or slightly decreased in recent years.[193] The Dutch government and the European Union have been striving for years to reduce reliance on chemical crop protection agents by promoting integrated pest management (IPM) in conventional farming and encouraging organic agriculture[194,195], though with limited success so far. [196,197] Research shows that a combination of various policy instruments targeting different levels (national and local) and cooperation with all stakeholders in the supply chain is most effective.[196,198-200] At the end of 2023, the European Parliament rejected a European Commission proposal to reduce the use of crop protection agents by 50%. To address the concerns of farmers, who are struggling to cope with numerous environmental measures, the European Commission withdrew the proposal in early 2024. As a result, the use of fungicides in agriculture in the EU is unlikely to decrease significantly in the coming years. Climate change may also impact the use of fungicides in various ways (including changes in crop choice, pest pressure, and product shelf life), but the net effect is unpredictable.

4.4 Recycling of fungicide-containing waste

The Netherlands and the EU are aiming for a circular economy by 2050. In a circular economy, as much as possible is reused and minimal waste is produced. For agriculture, this means optimising the use of residual streams. However, circular farming carries the risk of fungicides accumulating in the environment, especially when these are used on a large scale, as they currently are. Research from other countries points in this direction. For example, in neighbouring countries, the sludge from water treatment plants is spread over fields as fertiliser. In this way, large quantities of fungicides and antifungal agents (along with other pharmaceutical residues) end up in the soil.[70,201] In the Netherlands, treatment sludge is incinerated. Recently, however, orange peels have begun to be widely recycled and processed into animal feed and raw materials for food products for human consumption (see www.sinaasappelschillen.nl). The peels come from fruit that has been treated

after harvest with a wax coating containing antifungal agents, including imazalil (also known as enilconazole in veterinary drugs), to extend their shelf life. In these ways, fungicides re-enter the agricultural production and food chains. The Health Council has previously advised giving explicit attention to the potential risks of hazardous substances when recycling waste.[202]

4.5 Agricultural use also threatens the effectiveness of new drugs

A critical mistake was made with azoles when closely related compounds were used simultaneously as antifungal agents and fungicides, facilitating the development of cross-resistance. The same error threatens to be repeated with new antifungal agents due to the approval of new crop protection products based on closely related substances with the same new modes of action as the new antifungal drugs. As a result, these new drugs risk losing their effectiveness before they are even widely available on the market. Several new antifungal agents with unique modes of action, such as olorofim, fosmanogepix and ibrexafungerp, are currently in late stages of clinical development.[32,203-209] Olorofim is a promising new drug that could benefit patients with azole-resistant invasive aspergillosis.[210] Although olorofim is not yet available as a human medicine, a new agricultural fungicide, ipflufenoquin, with the same mode of action, was recently approved in the United States, Canada and Australia. In Europe, an application for its approval is pending.[26]

Laboratory research has shown that ipflufenoquin can promote resistance to Olorofim in *A. fumigatus*.[211] The concern that cross-resistance will become a problem in the future is heightened by the recent discovery that some azole-resistant strains of this fungus exhibit an increased mutation rate, meaning they may develop resistance to new generations of drugs more rapidly.[212] Two other crop protection agents, the fungicide quinofumelin[213] and the herbicide tetflupyrolimet[214,215], with the same mode of action, are also in advanced stages of development. Cross-resistance is also a looming concern with fosmanogepix.[26] This drug has a unique mode of action and is effective not only against azole-resistant aspergillosis but also against echinocandin-resistant invasive *Candida* infections.[216] However, an agricultural fungicide, aminopyrifen, targeting the same key enzyme, is also nearing approval.[217]

Experts recommend that before ipflufenoquin is approved for large-scale commercial use, field trials should be conducted to (1) determine the actual risk of *A. fumigatus* strains developing resistance to olorofim through exposure to ipflufenoquin and (2) identify high-risk applications that could result in the creation of hotspots for the development and spread of resistance.[211] In the United States, the Environmental Protection Agency (responsible for approving crop protection agents), the Department of Health and Human Services, and the Department of Agriculture jointly published an initial framework in late 2023. This framework aims to assess whether antimicrobial crop protection agents

could threaten the effectiveness of approved or developing drugs critical to human and animal health.[218] Stakeholders have been invited to comment on the proposal, with the ultimate goal of using this assessment framework for approving crop protection agents in the United States.

Currently, the approval procedures for drugs, crop protection agents and biocides are entirely separate. Legally, there appear to be few avenues to prevent crop protection agents from entering the market if they threaten the effectiveness of approved drugs with the same mode of action or of promising new drugs in advanced stages of development. Nevertheless, antibiotics are no longer approved as crop protection agents within the European Union to prevent the development of antimicrobial resistance via this route.[219] This may set a precedent for a similar regulation concerning the approval of fungicides with the same mode of action as drugs.

At present, there is no exchange of information between the approval authorities EMA, EFSA and ECHA in Europe regarding which substances are in the development phase, and the same applies to approval bodies elsewhere in the world. However, these three European bodies have recently expressed a desire to collaborate more closely on One Health issues, together with the EEA and the ECDC.[220,221] This may offer greater opportunities in the future to prevent the efficacy of crucial drugs from being compromised by chemicals used in agriculture.

4.6 Additional medical interventions for the prevention and treatment of fungal infections

The fact that severe fungal infections predominantly occur in individuals with weakened immune systems highlights the crucial role of a well-functioning immune system in controlling these infections. Over recent years, knowledge about how the immune system recognises, regulates and combats fungi has significantly expanded. This has opened up new possibilities to fight fungal infections by enhancing certain immune responses.[222-224] Various options are being investigated: therapies based on cytokines, genetically modified or non-modified immune system cells (T-cells, granulocytes) and monoclonal antibodies. However, significant challenges still need to be overcome for successful clinical application. Due to the high variability among patients, it is difficult to predict which therapy will be effective for a given patient. Additionally, excessive stimulation of certain immune responses can lead to severe side effects. Research is also being conducted into the development of vaccines to prevent fungal infections in at-risk groups.[223,224] Although no vaccines are currently available on the market, three are in clinical trial phases: two for *Candida* and one for *Coccidioides*, the causative agent of Valley Fever, which is endemic to the southwestern United States. Since *C. albicans* is part of the normal human gut flora, there is some concern about potential side effects of these early vaccines. A vaccine for *A. fumigatus* is still in the preclinical phase of testing.[225] Additionally, efforts are underway to develop vaccines that are effective against a broader range of fungi.[226]

These are also in preclinical phases. There is particular hope for the development of mRNA-based vaccines.[223,224] Since the natural microbiome plays an important role in defending against or regulating pathogenic fungi, manipulating this microbiome also offers potential in combatting fungal infections.[227,228] However, research in this area is still in its infancy. In summary, while there are promising opportunities to expand the limited resources available to physicians for the prevention and treatment of fungal infections, most of these interventions are unlikely to be ready for clinical use in the short term.

4.7 Ineffective policies

It has been known for at least fifteen years that the use of azoles as antifungal agents in agriculture is the main cause of increased resistance in *A. fumigatus* to closely related medical azoles, which has made the treatment of invasive aspergillosis significantly more difficult. In all this time, no effective policy has been established. For a short period, a protocol was in place requiring that waste heaps in the bulb industry be covered to prevent the spread of resistant fungal spores, but this was withdrawn when it proved ineffective, and keeping the heaps moist as an alternative measure was found to be practically unfeasible.

In the national approach to antimicrobial resistance, little attention has been given to the issue of resistance in pathogenic fungi. Since 2013, surveillance has been conducted on azole resistance in clinical isolates of *A. fumigatus.*[132] However, resistance development in the environment is not monitored by the government, although Wageningen University & Research (WUR) recently launched a citizen science project, the Schimmelradar (https://www.wur.nl/nl/project/schimmelradar.htm). In this project, citizens across the country collect *A. fumigatus* spores from the air and send them to Wageningen for resistance testing. Other fungal species, including Candida and Trichophyton, are not part of national surveillance programmes, and resistance development in these species is not tracked in the Netherlands. Emerging species like *C. auris*, *C. parapsilosis* and *T. indotineae* are also not monitored. Furthermore, there is no surveillance of fungal infections, meaning there is little knowledge about their prevalence or any shifts in occurrence. Finally, there is a lack of understanding regarding the use of antifungal agents, particularly because the extent of over-the-counter sales is unknown. The total sales of fungicides (including azoles) in agriculture are well-documented, but existing data on which substances are used, in what quantities, on which plots, for which crops, and at what times (each farmer is required to keep records for potential inspections) are not centrally collected or made available for research. The Health Council has in fact advocated for improvement of such usage data in the past.[229] Reliable data on the use of fungicides in biocides, for example in the preservation of wood, textiles and paint, are also lacking.

The lack of effective policy on antifungal resistance is due to several factors. First and foremost, health authorities, researchers and professional organisations continue to show relatively little interest in fungal infections. Between 2006 and 2018, 114 projects were funded under ZonMw's (the Netherlands Organisation for Health Research and Development) infectious disease control programme. Only one of these focused on fungal infections.[164] Since then, little has changed. At the Centre for Infectious Disease Control at RIVM, only a small group of experts is dedicated to fungal infections research. Furthermore, solving this One Health issue requires efforts from multiple Ministries, but no Ministry has been assigned responsibility for taking a leading role in driving the approach to this issue. This is also the case at the EU level and globally.

There are indications that this situation may improve in the short term. On 4 April 2024, the Minister for Medical Care informed the Dutch House of Representatives that the National Action Plan on Antimicrobial Resistance 2024-2030 will soon be presented. This plan, which all EU member states are required to prepare, focuses on continuity of existing policies and strengthening the One Health approach.
The plan brings together activities related to antimicrobial resistance from various ministries: the Ministry of Health, Welfare and Sport (VWS), the Ministry of Agriculture, Nature and Food Quality (LNV) and the Ministry of Infrastructure and Water Management (IenW). Three new priorities are emphasised: strengthening integration and collaboration both nationally and internationally, broadening the focus from antibiotics to antimicrobial agents – including bacteria, viruses, fungi and parasites – and expanding the focus to include the environment, including plants and water.[230]

05 advice

5.1 Conclusion

The committee concludes that the growing resistance of fungi to drugs increasingly undermines the treatment of fungal infections in humans and poses a serious threat to public health. The agricultural use of related antifungals in farming plays a significant role in this issue. The problem in many ways mirrors that of bacterial resistance to antibiotics, and action is therefore required. The committee bases this conclusion on the following considerations.

The disease burden of fungal infections is substantial

Fungal infections impose a significant disease burden. Relatively minor infections of the skin, nails and mucous membranes are very common. Approximately 250,000 people suffer from more severe, chronic fungal infections. Invasive infections, where the fungus invades organs or enters the bloodstream, are rarer, with around 3,000 cases per year. These typically occur as life-threatening complications in individuals weakened by underlying conditions or those undergoing long-term treatment with immune-suppressing drugs. These infections are difficult to treat. Moreover, treatment of the underlying condition must sometimes be temporarily reduced, postponed or halted. The risk of death is high.

Resistance increasingly hampers the treatment of fungal infections

Resistance to drugs for fungal infections (antimycotics) significantly raises the risk of death from invasive infections. As a result of resistance, superficial skin and mucosal infections could take on more chronic and disabling forms, especially since the arsenal of antimycotics to which physicians have access is very limited. If one class of medicine becomes ineffective, there are few alternatives left, which often have more side effects, are difficult to administer at home, and are more expensive. In the event of resistance to multiple or all classes of drug, infections become virtually untreatable. Due to the lack of treatment options, the impact of antifungal resistance is greater than that of resistance to antibiotics in bacterial infections. However, bacterial infections currently claim more lives because they occur more frequently.

In the Netherlands, approximately 10% of infections caused by *A. fumigatus*, a major cause of invasive infections, are resistant to treatment. For *C. albicans*, another key cause of invasive and mucosal infections, the resistance rate is lower, but its place is increasingly being taken by other resistant *Candida* species. Resistance in skin fungi, such as *T. rubrum*, remains rare. The same problems with these and many other fungal species are seen in neighbouring countries and globally. Resistance primarily affects azoles, the most important class of antimycotics, but is also increasingly seen with echinocandins and polyenes. Multi- and pan-resistant fungi are becoming more common.

Resistance primarily arises from agricultural fungicides

The resistance of *A. fumigatus* to medical azoles is mainly due to its exposure to closely related agricultural azoles and wood preservatives in its natural habitat, including decaying plant material such as that found in bulb farming and chipped wood waste. People become infected by inhaling fungal spores that spread through the air from these sources. The extent to which *Candida* species acquire azole resistance from environmental exposure is uncertain, but evidence suggesting an environmental contribution is increasing. Azole resistance in skin fungi such as *T. rubrum* is primarily attributed to medicinal use. Fungal resistance to echinocandins, polyenes and allylamines is almost entirely the result of medicinal usage, as these substances are (almost) never applied in other societal sectors.

The resistance issue is likely to worsen

The problem is expected to worsen in both severity and scale. The group of people at risk is continually growing due to factors like an ageing population, an increase in diseases that heighten susceptibility, and the growing prevalence of immune-suppressive medical treatments. Additionally, new contagious, multi-resistant fungal species – particularly *C. auris* and *T. indotineae* – have recently emerged. These species are already causing significant illness in other regions, are spreading rapidly worldwide, and have now appeared in the Netherlands. Globalisation and possibly climate change may have played a role in this. Efforts to reduce the use of fungicides in agriculture and for preservation purposes have stalled, and the recycling of contaminated waste reintroduces these substances into agricultural and food chains. Furthermore, new antimycotics like olorofim and fosmanogepix, which have been researched for years and are urgently needed to treat patients with resistant invasive fungal infections, risk losing their effectiveness quickly because related substances are simultaneously being released for agricultural use. Effective policies have yet to be implemented due to limited interest in fungal infections, fragmented and separate authorisation processes, and the absence of any designated national or international body to take the lead in addressing the issue of antifungal resistance.

5.2 Recommendations

The problem of antibiotic resistance has shown that, once resistance has developed in bacteria, it is nearly impossible to eliminate. This is likely true for antifungal resistance in fungi as well, making prompt action essential. Lessons can be drawn from the experience with antibiotic resistance, where the Netherlands has successfully implemented policies and is now viewed as a global leader. Recently, the Minister for Medical Care announced the *National Action Plan on Antimicrobial Resistance 2024-2030*, which will also focus on tackling antifungal resistance. The committee emphasises the importance of this and makes the following specific recommendations:

1. *Appoint a single coordinator*
   Assign the leading role of driving the approach to this issue to a single Ministry (VWS is the most logical choice, given its responsibility for antimicrobial resistance). This Ministry should work closely with other relevant Ministries (LNV, IenW, SZW), initiate or promote research (for instance, through ZonMw), coordinate measures and oversee progress. This follows the recent recommendations from the Social and Economic Council regarding cross-sector health policy and the 'Health in all policies' approach.[231]

2. *Better utilise and strengthen existing expertise on fungal infections*
   The Netherlands has an expertise centre for fungal infections, the Radboudumc-CWZ in Nijmegen. However, better use could be made of this expertise by physicians across the country for the optimal treatment of patients, not only in cases of acute invasive fungal infections but also in chronic infections such as chronic pulmonary aspergillosis and recurrent vulvovaginitis. Strengthen the infrastructure for fungal infections at RIVM's Centre for Infectious Disease Control, particularly for public health-related aspects such as surveillance and preparedness for potential outbreaks of pathogenic fungal infections. Consolidate existing expertise from various universities, medical centres and research institutes into a Fungal Diseases Knowledge Platform to improve the utilisation and exchange of knowledge on the agricultural, environmental, veterinary and health aspects of fungal resistance. A multidisciplinary approach, similar to that used for combating antibiotic resistance, could be similarly successful.

3. *Add fungi to existing AMR surveillance programmes*
   Expand existing antimicrobial resistance (AMR) surveillance programmes to include pathogenic fungi. It is important that this surveillance adopts a One Health approach, encompassing pathogen surveillance, disease surveillance, environmental surveillance (including chemical fungicides) and veterinary surveillance. Existing programmes, such as the surveillance of *A. fumigatus* in NethMap and the Schimmelradar project at WUR, can serve as models.

4. *Tackle sources of resistance proactively*
   Neutralise known hotspots for the emergence and spread of resistant fungi as quickly as possible. Investigate whether the collection and central fermentation of bulb waste and chipped wood could be an effective measure against the formation and spread of resistant *A. fumigatus* spores. Workers dealing with such sources should wear personal protective equipment. Conduct prompt research into other potential sources of resistance development in agriculture, livestock farming and the environment. Data from surveillance programmes (as per the previous recommendation) can assist in identifying these sources. Additionally, investigate whether common, toxicologically acceptable levels of fungicides in human food and animal feed could

induce resistance in *Candida* species within the gut microbiome.

5. *Minimise concurrent use of related substances in agriculture and medicine*
   Advocate within the European Union, and preferably globally, that active ingredients in new antimycotics, or closely related substances with the same mechanism of action, should not be used in the production of plant protection products or biocides. The EU has previously imposed such a ban for certain antibiotics.[219] If this is not feasible, require manufacturers of plant protection products and biocides to demonstrate, through risk assessments based on laboratory and field tests, that the proposed use of their product will not cause cross-resistance to related medicinal products in fungi that pose a danger to humans. At the EU level, address the need for effective and timely information exchange between the relevant regulatory authorities (EMA, EFSA and ECHA) and ideally beyond. This exchange is currently lacking.

6. *Promote Integrated Pest Management and antimicrobial stewardship*
   Further reduce the use of plant protection products and biocides in the Netherlands by promoting Integrated Pest Management (IPM). A combination of different policy instruments, aimed at various levels (national and local) and in collaboration with supply chain partners, is likely to be most effective.[196,198-200] In consultation with the relevant professional groups, promote the prudent use of antimycotics, especially in primary care, and limit the over-the-counter availability of certain antimycotics once surveillance data indicate that they are contributing to the spread of new resistant skin fungi, such as *C. auris* and *T. indotineae*. Antibiotics are also not available over the counter.

7. *Encourage research into additional medical interventions*
   Encourage (for instance, through ZonMw) research into additional medical interventions for preventing or treating fungal infections, such as vaccines, immune therapies or interventions targeting the microbiome. These could not only offer solutions where medicinal products are no longer effective but also provide opportunities to reduce the use of antimycotics and thus limit the development of resistance.

8. *Develop a national action plan for fungal diseases*
   Charge the newly established Fungal Diseases Knowledge Platform with developing a national action plan for fungal diseases. This plan should further elaborate on the actions already mentioned, as well as any additional necessary measures and indicate which stakeholders need to be in.

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[230] *Verslag (ongecorrigeerd stenogram) van een commissiedebat. De vaste commissie voor Buitenlandse Handel en Ontwikkelingssamenwerking en de vaste commissie voor Volksgezondheid, Welzijn en Sport hebben op 4 april 2024 overleg gevoerd met mevrouw Dijkstra, minister voor Medische Zorg, en de heer Van Leeuwen, minister voor Buitenlandse Handel en Ontwikkelingssamenwerking, over Mondiale gezondheidsstrategie.* Verslag TKO 2023-2024 2024.

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Committee and consulted experts[a]

Members of the committee on the Identification of Environmental and Health Issues for the advisory report *Resistance undermines treatment of fungal infections*:

- Prof. E. Lebret, Professor of Environmental Health Impact Assessment, Institute for Risk Assessment Sciences, Utrecht University, *chair*
- Prof. L. van de Grift, Professor of International history in relation to the environment, Department of History and Art History, Utrecht University
- Dr P.J. van den Hazel, Independent Environmental Health Expert, Physician Society and Health (non-practising)
- Prof. M. Huijbregts, Professor of Integrated Environmental Assessment, Faculty of Science, Radboud University, Nijmegen
- Prof. H. van Lente, Professor of Science and Technology Studies, Maastricht University
- Prof. J.P. van der Sluijs, Professor of Theory of Science & Ethics of the Natural Sciences. University of Bergen, Norway
- Dr E. Snelders, associate professor, Laboratory of Genetics, Plant Sciences, Wageningen UR
- Dr Y.M.R. Vendrig-de Punder, assistant-professor UMC Utrecht, Julius Centrum, dept. Public Health; Doctor Society + Health, Medical Environmental Science, KNMG
- Prof. F. de Vocht, Professor of Epidemiology and Public Health, Population Health Sciences, University of Bristol, United Kingdom
- Prof. F. Hagen, group leader of medical mycology, professor of Fungal Functional Diversity, Westerdijk Fungal Biodiversity Institute, Utrecht (an institute of the KNAW (Royal Netherlands Academy of Arts and Sciences)), *structurally consulted expert*
- Prof. P.E. Verweij, Physician-microbiologist, professor of clinical mycology, Radboudumc, Nijmegen, and expert on fungal infections, RIVM (National Institute for Public Health and the Environment), Bilthoven, *structurally consulted expert*
- Prof. A.P. van Wezel, Professor of Environmental Ecology and Scientific Director IBED (Institute for Biodiversity and Ecosystem Dynamics), University of Amsterdam, *structurally consulted expert*

Observers[a]:

- E. Haan MSc, Ministry of Infrastructure and Water Management, The Hague
- M.A. Hoorweg MSc, Ministry of Health, Welfare and Sport, The Hague

Scientific secretaries:

- Dr H.F.G. van Dijk, Health Council, The Hague
- Dr F.J.M. Mölenberg, Health Council, The Hague

[a] Consulted experts are consulted by the committee because of their expertise. Consulted experts and observers are entitled to speak during the meeting. They do not have any voting rights and do not bear any responsibility for the content of the committee's advisory report.

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).
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Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity.
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Erratum:
on 17 March 2025, several minor corrections were made to the list of members of the committee (page 54). We added the name of committee member Dr E. Snelders, who was accidentally missing. We also updated the affiliations of Dr P.J. van den Hazel and Prof. J.P. van der Sluijs, which were incorrect. These adjustments have no implications for the advice.

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