

Resistance undermines treatment of fungal infections

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 doctor. 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 doctors 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 the newly to be founded 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.

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