

One World, One Health Podcast
Episode 25, Season 1- Transcript
Guest: David Denning
When Fungal Infections Turn Deadly

Maggie Fox (0:01)

Hello and welcome to One World, One Health, with the latest ideas to improve the health of our planet and its people. I'm Maggie Fox.

Planet Earth faces problems such as pollution, climate change and new and reemerging infectious diseases and they are all linked. This podcast is brought to you by the One Health Trust with bite-sized insights into ways to help.

They're living on your skin, inside your body, in the air around you and in the soil. Fungi are everywhere and they're usually benign. At the worst, most people think of fungal infections as causing mild conditions, such as thrush in the mouth or athlete's foot. But fungal infections can kill.

In this episode, we're chatting with Dr. David Denning, a retired professor of Infectious Diseases at the University of Manchester in Britain, who's the founding President and Chief Executive of Global Action for Fungal Infections, or GAFFI. GAFFI estimates that fungal infections kill 150 people every hour around the world. They can cause blindness and deformities, and more than 300 million people have a serious fungal infection of some sort.

The HBO series *The Last of Us* has brought attention to the possibility of dangerous fungal infections, although it's a highly improbable, fictionalized scenario. Dr. Denning is here to talk about the very real risks and possibilities.

David, thanks so much for joining us.

David Denning (1:27)

It's a pleasure, thank you for the invitation.

Maggie Fox (1:29)

First off, let's talk about some of these various infections. There's a wide range of them, I think.

David Denning (1:34)

There are many different sorts of fungal infections. Some fungi, which cause disease in humans, cause different infections. So you can get oral candidiasis or vaginal candidiasis and

you could also get it in the bloodstream. There are other fungi that cause individual infections, a single infection, and so it's a little bit easier and an example of that is *Pneumocystis pneumonia*.

Maggie Fox (1:53)

And that's something that affects people with HIV, I think.

David Denning (1:57)

Yeah. *Pneumocystis pneumonia* is a life-threatening infection in people with HIV, advanced HIV disease, but it also is a problem in people with some cancers and transplant patients as well. And it was described in malnourished children and sometimes occurring in children in poorer parts of the world as a *de novo* illness as well.

Maggie Fox (2:18)

And some of these pathogens that you name, they're not necessarily pathogens, right? They're benign colonizers. I'm thinking of *Candida albicans* and other fungi like that.

David Denning (2:29)

You're quite right. *Candida albicans* lives in most people's bowels. We don't even know it's there, it's not a problem at all. But if you're very sick, or get in a big car accident and end up in critical care, or have a lot of antibiotics or have diabetes, it can actually enter through the gut and go around the blood, causing a bloodstream infection. And most people don't even know they've got it and it isn't a problem for them, as you rightly say.

Maggie Fox (2:51)

And what happens to make these organisms turn bad?

David Denning (2:55)

A lot of that's about what's wrong with the person, but not completely so. Many women who get yeast infections, or candidiasis, are completely normal women. There's absolutely nothing wrong with them. They just get an overgrowth of *Candida* and it causes a yeast infection. And there's a group of women who get that recurrently, so they can have four or more episodes a year, and a very small number of women seem to have it almost continuously and it's a real problem. So it's mostly affecting women in their fertile years. But post-menopausally, if you're on HRT, it can come back and cause a problem in those people as well. So these people are completely normal.

The other people who are completely normal who get fungal infections are those who get a fungus penetrating the skin or in their eye. So if you have some dust in the eye related to, for

example, threshing of wheat, and it's got a fungus on it, you can get a fungal eye infection, which can be devastating for vision in that eye. And in many parts of the world, farmers get a prick from vegetable matter and that can cause a low-grade but serious and chronic infection of their skin and occasionally in their bones as well. And they are completely normal, they just can't defeat this fungus at all.

Maggie Fox (4:07)

Now, the World Health Organization has designated a few fungal infections as being of critical or high importance. Can you tell us why that matters?

David Denning (4:16)

There were four at the top of the critical list: *Candida albicans* which we spoke about, which is really very common. And if it does get into the bloodstream, even with our current drugs, still around 40% of people die of it. So it's a very serious infection. *Candida auris* is a multi-drug resistant *Candida* which also can get into the bloodstream and causes outbreaks in hospitals. It acts a bit like a bacterium in that it goes from one person to another in a hospital setting, and it sticks to catheters and other plastic ware. And it's a new fungus, but is multidrug-resistant. So that's a tricky fungus.

Aspergillus, that I've mentioned, is top of the list. The reason that that's there is because it's really quite a difficult diagnosis and the drugs are completely ineffective and there's resistance that's out there and I'll talk a bit more about that. And then the other one that's top of the list is *Cryptococcus*, which causes meningitis, particularly in patients with HIV but also in transplant and lymphoma patients, and occasionally normal people as well. There's a group of people in Southeast Asia in particular, but it can be anywhere, who seems to get this pneumonia plus meningitis. So that's a really horrible infection that they get it.

Maggie Fox (5:25)

And you've mentioned two important points here: that other infections can make people more susceptible to these fungal infections, and then these fungi can themselves evolve resistance to the drugs used to treat them. There's tuberculosis, there's HIV, but then there's COVID. Right? Let's talk about what COVID has done. It's been causing this infection called black fungus, or I think it's pronounced mucormycosis, which was a problem in India.

David Denning (5:50)

Mucormycosis has been known for a long time, it's a bread mold amongst other things. And again, usually, if you're normal, you would not get diseased with it. But we do know that if you have significant diabetes, then you can get life-threatening mucormycosis.

What happened in India with the outbreak? I should say, there's already much more mucormycosis in India than anywhere else in the world. We're not quite sure why that is. What did happen during COVID is there weren't enough beds for people who were sick, they were triaged in the emergency room, given steroids and sent home. Those steroids were often given in too high a dose for too long and they would sometimes precipitate diabetes. People who either had diabetes or developed it for the first time because of the steroids.

The combination of COVID plus steroids plus diabetes meant that tens of thousands of people in the space of a few months caught mucormycosis, which is unprecedented. We've never ever had an outbreak of that size of severity anywhere in the world before with that fungus.

Maggie Fox (6:52)

Are there drugs available to treat it?

David Denning (6:54)

Yes, none of them are perfectly effective and you almost always, 99% [of the time], need surgery for mucormycosis as well. The surgery can be quite a devastating surgery. One often has their whole eye removed, for example, and things like that. It's really pretty dire, some of the outcomes from mucormycosis. If you survive it, it's really a lot of damage done sometimes.

Maggie Fox (7:16)

And this surgery that people have, it's to cut out big pieces of infected tissue?

David Denning (7:21)

Yes. Because the fungus blocks the blood vessels, and so the tissue dies, and then it thrives in dead tissue, so you need to get rid of the dead tissue. Otherwise, you leave fungus there. You need to cut the dead tissue out and leave just a clean margin and it goes straight through bone, straight through nerves. It doesn't seem to respect any tissue planes whatsoever. It's a really difficult infection, actually.

Maggie Fox (7:44)

And although there are drugs, your organization is advocating for the development of more and better drugs. Why is that needed?

David Denning (7:51)

Well, we know that the response rates to current drugs is less than perfect, as I mentioned. With *Candida albicans* in the blood, you've still got around 40% mortality. You've got typically a 50 to 60% mortality for invasive aspergillosis. So the drugs are not perfect. Then you have resistance

on top of that, which means the drugs don't work at all. And that's particularly true with resistant *Aspergillus* and *Candida auris*.

We've also got other problems related to drug-drug interactions and other things, which means that it's difficult and [there are] side effects from limits. So it dumped some difficulties in treating some patients as well.

I should say that GAFFI's primary core is actually for everybody across the world to have access to the current drugs, because if you could make the current drugs available to everybody, that would have a very big impact. And then you could then add the new drugs when they come through on top of what is already there.

There are many, many people across the world who don't have access to the current drugs at all, or they're not paid for as part of a health system. There's no insurance or the insurance doesn't cover it. Some people ended up being completely impoverished as a result of having a fungal infection.

Maggie Fox (8:59)

One of the other things you advocate for is testing in the first place so people even know they have these infections.

David Denning (9:05)

Yes, we're very keen on adequate diagnosis of fungal disease for many reasons. First of all, it's important to know that you have a fungal infection, because you can't treat it with standard antibiotics. That's the number one thing.

It's also important to rule out fungal infection. And the tests are pretty good at that. They're not perfect, but they're pretty good at that. [That] means you don't need to take antifungal therapy if you don't need it and have the toxicity attached to it and the cost attached to it.

There are many, many countries in the world which have a limited number of these diagnostics and they're not terribly expensive. There's been a fantastic improvement in the quality and the sensitivity of diagnostics in the last five or six years. There should really be no excuse, other than possibly economics, for people not having these diagnostics out there.

Maggie Fox (9:48)

And what about vaccines? Are there vaccines against fungal diseases?

David Denning (9:51)

There are no fungal vaccines. There was one developed by a group in Los Angeles which was trialed in women with recurrent vaginal candidiasis and it was partially effective and thought to be quite useful. It also, because of the molecule that it worked against, might have prevented staphylococcal infections as well. But to my knowledge, it hasn't been taken through to clinical usage and commercialization. There are other difficulties, generally, because many of the people with the most severe infections have a damaged immune system. So if you have a damaged immune system, you don't respond very well to vaccines.

There are limitations, I think, on how effective a fungal vaccine would be to prevent life-threatening infection. Having said that, there are people who could be immunized. If you are waiting for a lung transplant, kidney transplant or a bone marrow transplant, you could be immunized before you have the transplant and prevent you getting an infection afterwards. There are groups that could be protected, I think, but having a really, really strong immune response, which protects people, is important.

Maggie Fox (10:49)

Now farmers have to fight fungal attacks on their crops, but has the use of agricultural fungicides helped lead to the rise of antifungal-resistant bugs like *Candida auris*?

David Denning (11:00)

Ninety percent of crop diseases are fungal. Whereas in humans, we have a lot more viruses and bacteria, and fungus is less important, with the possible exception of skin. In crops, it's 90% fungal. We sprayed the crops with multiple different antifungals, or fungicides as they're called. Some of those had the same molecular structure as the ones we use in people and as a result of that, we've got an increasing amount of resistance in *Aspergillus*, where the azole fungicide allows, as a sort of bystander effect or collateral damage if you like, in the soil, a fungus that's resistant to emerge. And then when that soil is disturbed, it gets into the air and people breathe it in and they can be infected with a completely resistant fungus.

Maggie Fox (11:42)

If farmers have to fight resistance, it implies that there are new fungicides being developed. Are there some that are concerning to you?

David Denning (11:51)

There are a couple of new molecular structures which are starting to be developed and being used and one of them has just recently been approved. Unfortunately, it's this very similar molecular structure with the same target and side fungus that's also going to be one of the new antifungals that's supposed to be out there as a resistance buster. So we're in a very unhappy situation where for crop use, a new antifungal was coming through that may well have the same story with resistance as we've got for people with clinical disease caused by *Aspergillus*.

Unfortunately, the people who regulate and approve new fungicides don't require at the moment any testing on human fungal pathogens as part of their portfolio of work. They worry a lot about whether they're toxic, whether they spray, what they work for, and all of those things. But they don't ask the question, "Is there a bystander effect on Aspergillus in particular, but also other fungi?" And they should be asking that, in my view.

Maggie Fox (12:44)

Is there something that the average person can do to fight this problem?

David Denning (12:49)

Well, fortunately, most people don't get a fungal infection. In terms of their own personal health, there aren't any specific diets or other things that are necessary to avoid fungal disease. If one is ill or a family member is ill, if they are particularly severely ill, it's very helpful for family members and the patients affected to say to the doctor, "Could it be a fungus?" To ask the question explicitly, because the tests are different tests, they're not the same test. Sometimes, doctors forget to ask for those tests or don't know which tests to ask for that they can seek advice.

On a general, perceptual level, we talk about antibiotic resistance, but we really want to talk about antimicrobial resistance, because it isn't just antibiotics or antibacterial agents. It's welcomed that CARB-X in the US has taken on antifungals as a new area to put support into because I think it's very much needed.

The other area from a global perspective is the area of severe asthma. There's a very large number of people around the world who have severe asthma. If you're in the US, you can afford to have one of the biologics, which costs \$25 to \$40,000 a year. But people in many parts of the world cannot afford those. Because it's a biologic, the price is unlikely to come down very, very substantially as the case with those generic drugs. That leaves lots of people around the world without good treatment for severe asthma except for steroids, which have lots of side effects.

Antifungal therapy is useful for those people. So, there is an opportunity, I think, for significantly large numbers of people who have severe asthma to benefit from antifungal therapy across the world. It's a much bigger problem than people see, the public had not terribly been aware of these things. They've heard of Athlete's foot and yeast infections, but the rest of it they don't know about.

Maggie Fox (14:42)

David, thank you so much for taking the time to chat with us today.

David Denning (14:47)

Good. Thank you for the opportunity.

Maggie Fox (14:49)

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