Erta Kalanxhi
0:00
Good morning, good afternoon, and good evening everyone. Thank you very much for joining us today. My name is Erta Kalanxhi and I'm a Research Fellow at One Health Trust. We only have one hour for this discussion so this introduction will be to the point. Our discussion today will focus on fungal infections and the burden that they impose on our health and well being.

While severe fungal infections are rare, compared to the uncomplicated, superficial ones we usually or most of us are familiar with, they can be deadly as well. In the backdrop of climate change, a growing population, and the increased risk for future pandemics, this is a very important issue to discuss and they cannot be ignored, the reason for that being that currently, we are not well prepared to diagnose them and treat them. So for the past year, we have been talking to experts from different fields and we have discussed some of the gaps, challenges, and opportunities that arise to address them.

Some of these experts are here today and I want to thank them in advance for their dedication and their support. Joining us today, we have Professor Malini Capoor from Vardhman Mahavir Medical College and Safdarjung Hospital in India. We have Professor David Denning joining us from the University of Manchester in the United Kingdom. We have Dr. Ana Alastruey Izquierdo from the Instituto de Salud Carlos III in Spain. And we have Dr. Hatim Sati from the World Health Organization.

Thank you again for taking the time to speak with us today. Before we start the discussion, I just wanted to go over practical information. We will spend the first 45 minutes having a discussion and highlighting some important issues with the experts. We obviously are not going to be able to cover everything. But we will have about 10 to 15 minutes at the end of this webinar to answer some of your questions. So if you do have them, please send them in the Q&A section in the Zoom app. We'll also share a few relevant articles or reports that will complement the discussion today. I look very much forward to this discussion and we'll start right away because the time is passing. So we'll start with Dr. Capoor. Dr. Capoor is joining us from India and she is a Professor in Microbiology and a leading expert in mycology. Dr. Capoor, thank you for joining us.

Malini Capoor
3:15
Thank you, Erta, for a gracious introduction. Hello, everybody. Greetings from India.

Erta Kalanxhi
3:21
And greetings from Ivory Coast. That's where I'm based and just to let you know in general, our audience today is very international and I can say that there are many countries represented here today. As I mentioned earlier, fungal infections, they can differ greatly in the way they present and in their severity, and many of them are considered as Rare and Neglected Diseases. But during the COVID-19 pandemic, this rare disease, also referred to in a popular form as the black fungus, was responsible for thousands of

cases and deaths. There were several outbreaks during that time. Can you tell us how this played out, what is this disease, and why were there so many deaths in India during that time?

Malini Capoor
4:18
You're absolutely right, Erta. Fungal infections, they differ greatly in presentation and severity, from superficial to deep seated and angioinvasive fungal infections like mucormycosis, and even in cases of superficial fungal infection, you take the example of dermatophytosis: if there is irrational use of steroids, it can also land up in epidemic proportions, [like] what we had...a great Indian epidemic of dermatophytosis. We all know that mucormycosis is the third most common invasive fungal infection. But during the COVID-19, there was an unparalleled upsurge in mucormycosis cases in India, especially during the second wave of COVID. To be precise, that was from April to July 2021. In fact, it was a tsunami more than a deluge, I would say, although the concern about mucormycosis in India is not new, if you compare the pre-COVID data and during COVID.

But during COVID, it was more than 50,000 cases -- to be precise, it was 47,000 cases as per the Government of India website and it clearly mentioned that the cases could be more. India, we know that it is the diabetic capital of the world, but it was mainly the uncontrolled diabetes and the misuse or the irrational use of steroids. The factors are well known whether it is uncontrolled diabetes or hematological malignancies, neutropenia, solid organ transplant, burns, trauma, immunosuppressants like corticosteroid therapy, and non adherence to the infection control practices, these are well known factors. But if you compare the pre-COVID data of mucormycosis from the Indian healthcare facilities, this increase was due to an increase in the interventions. How from one particular tertiary care center, from 24.7 cases annually, it increased to three times what it was pre-COVID?

Then, if you compare the Indian prevalence, it is 70 fold greater than that of the global prevalence. And during COVID, as I've already mentioned, during the second wave that was from April to July [2021], there was a tsunami of cases: 47,000 cases of mucormycosis. For diabetes, I would say it's poorly-controlled hyperglycemia induced by steroids and because a large number of COVID-19 patients were taking other prescriptions or over-the-counter drugs also, [like] glucocorticoids, immunomodulators, unsupervised due to the excessive caseload, which likely contributed to the epidemic.

We are all aware that corticosteroids are used in [COVID] management, they can lower the mortality in individuals with severe disease, especially in cases of oxygen shortage. The Government of India, also due to oxygen cylinders shortage during the second wave, [released] a guideline [on] when to use [corticosteroids], but, there was an irrational use of steroids because of increased caseload and, but everybody is aware that [steroids act] as a double-edged sword. It impacts the neutrophil migration endocytosis and the COVID-19 and its treatment also may accelerate the cellular development of COVID-19-associated mucormycosis.

There are certain protein receptors like the spore coat protein CotH present in Mucorales, they initiate the infections by binding to the endothelial scepters. These receptors' expression is raised by the host variables, especially associated with diabetic ketoacidosis, ketone bodies, high glucose concentration and there was uncontrolled diabetes and steroid-induced hyperglycemia which led to this epidemic and there are a large number of studies from India, and even a study from our center, which support [the idea that] it was the irrational use of steroids and immunomodulators due to excessive caseload.

Already our public health care facilities are loaded with patients. India is heterogeneous as far as the topography is concerned and the healthcare facilities, we have the best of the centers. Then we have the primary health care centers. There is a study with the Reference Center and other centers…in 2023. They also corroborated that it was uncontrolled diabetes and hyperglycemia induced by steroids. Few studies have quoted zinc supplementation also; basically it is COVID-19, steroids, and hyperglycemia induced by steroids, and uncontrolled diabetes mellitus because people were not visiting the hospitals during that time. Then the Government of India also declared it to be a notifiable disease. There is already a low doctor:patient ratio because our population is quite high and the COVID-associated mucormycosis prevalence was 0.27% amongst hospitalized patients.

So, I would end the discussion with the unholy trinity of diabetes, and the rampant and irrational use of corticosteroids, and over the counter availability of these drugs. Amid COVID-19, especially during the second wave, our caseload was very high, it was near the USA [numbers] and appears to increase the occurrence of mucormycosis. Though the concern about mucormycosis is not new, as far as India is concerned, but during the second wave, it was a deluge. Thank you.

Erta Kalanxhi
10:45
Yeah, thank you so much for getting into the details and the specifics of how the COVID-19 pandemic created the perfect storm for the outbreak of mucormycosis in India. Given the challenges or the issues with diagnosing fungal infections and the lack of access to health care, where the burden is highest, this may be the tip of the iceberg in India.

Malini Capoor
11:15
Exactly, because we are a tropical country and our spore count is also very high indoors and outdoors, and then we have overburdened care because of the population. There are a lot of other rare fungal infections also coming up.

Erta Kalanxhi
11:38
It is clear how something that is rare can be not rare anymore, rare no longer, if I can say that. What implications does it have for future pandemics and do you think that India is ready? Of course, it is difficult to address all the issues that are there, but with regards to this particular outbreak, how is the country prepared now and what kind of implication does this have for future pandemics?

Malini Capoor
12:10
Yeah, the Government of India, after this pandemic, has created seven Indian Council of Medical Research Centers of Excellence for Mycology, apart from the two WHO-recognized or the ECMM-recognized centers we already have. One is at PGI Chandigarh and the other one is at Patel Chest. Seven Centers of Excellence for Mycology are in the various zones of India. The Government of India also developed a portal that was created at the National Centers for Disease Control and was linked with the integrated disease surveillance program. It made mucormycosis notifiable.

Then, as per the National Medical Council, there's a pandemic module added to the curriculum of the medical graduates and the post graduates wherein the five common fungal infections we teach -- we were teaching them the theoretical aspects of the common fungal infections -- how to diagnose them, especially the second year undergraduate medical students. After studying microbiology and the fungal infections in detail, they have been asked to diagnose especially when they are posted on the clinical site during the medical school. Like in the ENT, or Otolaryngology, posting, they have been asked how to diagnose a case of mucormycosis invasive aspergillosis. So, one of the five diseases they have taken up is aspergillosis where the disease burden in India is high. Aspergillosis, cryptococcosis, mucormycosis, and also dermatophytosis: they are asked to teach how it appears on the microscope and how they can diagnose, because these medical graduates practice as part of their internship program or the rural posting program. In the outreach center, they are able to diagnose on the microscopy aspect, the basic facility aspect, and then there are certain India-specific guidelines which are nothing but ISHAM and the ECMM guidelines.

The Fungal Infection Study Forum is there, the ISMM Society for Medical Mycology is there, and the Indian Council of Medical Research and the Ministry of Health and Family Welfare [are there]. Fungal infections are in focus. Everybody knows that fungi have been surviving on this Earth [for] billions of years. They have survived the asteroids, they have survived the pandemics also, and played havoc during the pandemic. They are an important part of climate change. So now the Government of India is also focusing on fungal infections and have added to the medical and the undergrad curriculum, the practical aspects and the management part of it, and has opened the Centers of Excellence for diagnosing it further, apart from the two WHO- and the ECMM-recognized centers.

The clinicians and the microbiologists, they act as a team, they work in a team and for better diagnosis and management of fungal infection. One good thing [that] has happened is that the WHO Essentials Diagnostic List has come up, wherein there are lateral flow assays for the three common fungal infections in India like cryptococcosis, aspergillosis, and histoplasmosis. The government also has a plan of initiating these tests in the centers across India. This good thing has happened and especially these kinds of webinars that One Health Trust is [holding] for better awareness about fungal infections and lots of clinicians and microbiologists have joined around the world.

Erta Kalanxhi

16:15
Great work. Thank you so much for your very detailed insights. I think for the sake of time we are going to [move on]. I know there's a lot more to say and thank you for sharing that from India. We're going to move on to Dr. Denning. Dr. Denning, thank you so much for joining us today. Dr. Denning spent his entire career working on global health and medical mycology. He's the founder of Gaffi, Global Action for Fungal Infections, which not only brings awareness to these infections, but also advocates for access to diagnostics and treatment for everyone. So thank you so much again for joining us. I will highlight the issues with diagnosis. During our earlier conversations and roundtable discussion, somebody said that fungal infections exist where there is a mycologist. I thought that was a very well said and interesting saying. They are hard to diagnose and hard to treat. Could you please highlight some of the most important unmet needs in the clinic regarding both diagnosis and treatment? Where are we today?

David Denning
17:38
Sure. So fungal infections, generally, there are some exceptions, are less common than bacterial and viral infections. And therefore, it's very easy for people to ignore them and think that they've done a good job because they've recognized a [bacterial] infection, they've treated it with antibiotics, and many patients will get better and that's great. The problem is that many of these fungal infections are lethal if they're not diagnosed and treated. So it's really important to, even though they're less common, to pick them up and treat them. And it's made worse, that problem, because they're often co-infections, so you can have two things together or three things together. So it isn't just using Occam's razor, like if you've diagnosed *E. coli*, therefore, you can forget about everything else, you can have *E. coli* and *Candida*. Or you can have tuberculosis and histoplasmosis, or they can be mistaken. There's an issue of co-infection and mistaken infections.

The real way to focus this, and I'm going to leave out of this discussion skin infections because that's a separate topic area, is that it's mostly the patients at risk that need to be studied in detail. Those are the patients in ICU, leukemic patients, patients with cancer undergoing chemotherapy with strange syndromes, funny lungs, and pneumonia, who may have pneumocystis or aspergillosis, patients on dialysis, diabetic patients, late-stage HIV patients, and patients who aren't getting better from tuberculosis, patients with asthma that's poorly controlled despite doing the normal things, we're giving them some steroids and steroid inhalers. There's a discrete group of at risk patients, and they're the ones that need the diagnostics. If you're in an emergency room and you have a child that comes through the door who's a bit sick, that's not a child that you would normally do a fungal diagnostic on. But all these other groups, in which there's quite a lot of people, are the ones that really need the care. The challenge for us is the health system where those things sit.

In Africa and other parts of the world, patients with HIV may present for the first time in a local community clinic and they don't have the ability to diagnose cryptococcal disease or histoplasmosis or pneumocystis, in many circumstances. They'll often infer the patient has TB, because that's relatively common, treat the patient for TB, and then by the time the patient has arrived at the hospital, the local

hospital or a teaching hospital, it may be too late to save them from the fungal infection, which is actually the primary problem that they've got.

One of the great needs here is where to do these tests, and where in the health system do they fit. And my view is that all of the WHO listed essential diagnostics should be available in all teaching hospitals, in every country, across the world. That should be just absolutely completely and utterly routine. If you call yourself a teaching hospital, you need to be able to diagnose vulnerabilities, come what may. There's a dialogue about a bit further down the health system in the bigger district hospitals, which tests are appropriate in that setting? Microscopy is cheap and easy and that should be available everywhere, in my view. Fungal culture should be available everywhere. Some of the more sophisticated tests like cryptococcal antigen should also be available in those types of settings.

I think that's what we should be aiming for. We have been so blessed in the last 15 years, with a wonderful set of new, relatively rapid, relatively inexpensive, and pretty high performing diagnostics for fungal disease. The best is, of course, streptococcal antigen lateral flow assay, that's a fantastic test. But there are many others that are pretty good as well. They just need to be factored into every health system and reused, alongside education, laboratory education, and the political educational.

Erta Kalanxhi
22:15
Thank you. Thank you so much, David. What about with regards to the development of new antifungals and treatments that are currently available? It is difficult to design new antifungals because of many biological and other factors. But with regards to the one of the later stages of development, clinical trials, could you please highlight some of the issues? Because I think that that's a very important step to be discussed, given how we consider these diseases to be rare. And they may be rare in some populations and not in others, so how does this complicate the development in the later stages of drug development?

David Denning
23:13
We have a reasonable portfolio of current antifungal drugs, but there are some countries that don't have them. And that's the first problem. It's not what you've asked me about. But it is important that before one starts developing new things, at least the old things are available everywhere.

We need new drugs because we've got quite a lot of resistance. In *Aspergillus*, there's quite a lot of resistance, we've got *Candida auris*, which is a multi drug-resistant candidate infection, and often [*Candida*] *glabrata* is resistant, we've got organisms that are intrinsically resistant, such as Fusarium, poorly responsive to many things. We do definitively need new antifungals.

We also have underperforming antifungals. If you give fluconazole for cryptococcal meningitis, only about one in three of your patients will be alive after six months. That's inadequate therapy, it doesn't work very well. If you give amphotericin and flucytosine together, you can push that up to 60 or 70%

response, but it's not 100%. So how do we get to 100% or 95%? How can we rise up to that level? And that's where the new drugs come in, in particular.

Historically, these drugs have been licensed for invasive candidiasis or candidemia and invasive aspergillosis. There hasn't been a new registration for cryptococcal meningitis or histoplasmosis for three or four decades. We haven't just haven't seen a drug that's come through for those other areas. So they tend to be developed just for *Candida* and *Aspergillus* infections, and then the other infections get added on. Maybe it's got activity on this, and so the little study is done. The confidence about how these drugs actually work in these other settings is not so great. To prove a drug is safe and works, you've got to study probably 1000 to 1200 people with the new drug, and that's after you've got through all the difficulties of preclinical and phase one and all those things. Then you've got to show at least equivalent efficacy, and that's quite difficult to do. Superiority is particularly difficult to do in statistical terms, so these studies are big and expensive, and complex to do.

The group studying cryptococcal meningitis across the world, groups I should say, have been remarkably successful at raising public funding. But that's the only fungal disease where public funding of significant amounts has been put in to do randomized controlled clinical trials. We need public funding, I think, for some of these other infections to be able to study them. Fungi in humans are fairly similar. We're all eukaryotes, finding the exact target within the cell that kills the fungus and doesn't kill a human is a little tricky, but there are lots of targets to do that. In fact, that's not the primary problem. I think it's taking them from there, all the way through to the end of clinical is actually what the biggest challenge is. I would really like to see some real good public funding and a really good clinical trial that works for these other diseases coming through.

Erta Kalanxhi
26:53
Thank you so much, David. I think you sort of prepared the way for our next topic, which is antifungal resistance. And for that, we have Dr. Ana Alastruey Izquierdo, joining us from Spain. Thank you for joining us today. A lot of your research has been focusing on antifungal resistance. Could you tell us something about it? You have everything on the go?

Ana Alastruey Izquierdo
27:25
Thanks very much. Can you see my screen?

Erta Kalanxhi
27:29
Yes, we can see it.

Ana Alastruey Izquierdo
27:30

Thanks very much, Erta. I'm very, very happy to be here and to be with such a big audience. So I would like to use this opportunity to remark on some of the things that my previous colleagues have said.

One of the problems is the lack of diagnosis, but whenever we have a diagnosis, how do we treat the patients? We only have four classes of antifungals available. These are polyenes, pyrimidins, azoles, and echinocandins, and most of them have different problems. Not only toxicity, because as you know, one of the problems is that fungi have eukaryotic cells the same as we have, so that's one of the reasons why it is difficult to develop new antifungals, but they [also] have drug-drug interactions. Sometimes you need to do TDM to check that the level of antifungal in the body wherever the infection is happening is correct. Some of them are only an IV treatment, for example, the echinocandins, they are somewhat restricted, as David was saying. The problem is that even if they are good, you treat the patient and they are not responding very well.

Just to give a couple of examples, David has touched on this already. There is now, in the last [few] years, emergency antifungal resistance. It was first with azole-resistant *Aspergillus fumigatus*, which started to be a problem in 2008. We've seen that the increasingly azole-resistant *A. fumigatus* has been enormous in the last few years and you can see them all around the world. But also as David was saying, there has also been a development of echinocandin-resistant *Candida glabrata* which is usually already resistant to azoles, so that limits you to mainly only Amphotericin B to be able to treat this species. Lately in *Candida auris,* which has been a pandemic, it's been appearing in all different countries. It causes nosocomial infections [that are] very difficult to treat because it's the first Candida that is pan-resistant. The isolates are found resistant to all antifungals. There are many other intrinsic resistant fungi such as *Fusarium* and other species.

We've seen that there is not much data about [antifungal resistance], because luckily we are still not in the ranges of antibacterial resistance, so there is not that much rate of resistance. But we don't want to get to that, right? We want to act now because we can and we can do something. There's not that much data, but some of the papers that have been published say that whenever you have a resistant strain, the mortality increases a lot. Susceptible strains, the mortality could be between 30 to 50%, while [it could be] 88% in these resistant strains, this is just an example.

You can also see how the use of antifungals in the clinic has an impact on the epidemiology. So what you would say, and I liked this very much, because what you see here is that when you have the epidemiology. Fungi are all over the world, when you breathe, you are breathing fungal spores. They are on your skin, they are [in] your mouth, [in] your nose, [in] your intestinal tract, they are everywhere. Whenever you treat with an antifungal -- the same as it happens with an antibiotic -- you change the community that you are having there. If you treat with [antifungals for] more than seven days, you have a different epidemiology and you will have different species. This completely relates with the pattern of resistance. It's very important to do antifungal stewardship or control with the antifungal you are using. And we are only talking about the clinic now. I think we can talk about the One Health approach later, but this is more or less what I wanted to say in this regard.

Erta Kalanxhi
31:56
That is a very important point because antifungals are not only used in the clinic, they are also widely used as pesticides in agriculture. And could you please elaborate a little bit on this connection between the two and if there is an impact?

Ana Alastruey Izquierdo
32:14
Yeah. I knew you were gonna ask this because we are now facing a real One Health challenge here. So, while in other places, there is not that [much] and maybe some fungal infections are not that [prevalent], but fungi are mainly pathogens of plants. Most of the fungal infections that we know are in plants. We use fungicides everywhere in the world to try to not develop these infections in plants, so they are used everywhere. We've seen that the fungicides that are used in agriculture are very similar to the ones that we use in the clinic. So, it has been demonstrated that the use of fungicides in agriculture develops resistance in the environment that is able to cause infection in the clinic. It's a real One Health thing.

There have been two roots of antifungal resistant development in *Aspergillus fumigatus*. One is the use of fungicides in agriculture and also lung treatment in the clinic. An important thing there is that we've seen that in the environment, we have very big hotspots. If you think about fungi, where would you find fungi? Well, wherever you have humidity and you have some warmth. This is a perfect storm when you do the compost in the environment, whenever there is agricultural practices, if they are full of fungicides, and then it is warm and humid. There will be a complete overgrowth of fungi with the pressure of the fungicide, so they develop these resistance then they produce spores and these spores are everywhere. Everybody inhales them, and if you get sick and your immune system is not working properly, then you can develop an infection.

Erta Kalanxhi
34:38
Thank you, Ana. That's incredible. Thank you very much for these slides. I think we're moving along really well. I'm sure that there are a lot of questions that we can address later on. But we'll move on as well with Dr. Sati, who is joining us from Geneva. He has done some very important work at the WHO with regards to the Fungal Priority Pathogen List which came out last year. Now, this has been a very important development as the list was the first of its kind, so in addition to bringing awareness to the issue, it also has identified some specific gaps in the field. Dr. Sati, thank you for joining us. And perhaps you could talk about some of these gaps that you identified.

Hatim Sati
35:30
Thank you. Thank you, colleagues. Thank you for having me. And indeed, as you mentioned, the last major exercise to prioritize fungal pathogens was conducted over two years with the participation of a broad range of stakeholders and experts on this call. Ana and David were crucial to the completion, Ana

is the chair of that working group. Through that process, we were able to identify a lot of gaps in terms of knowledge, in terms of evidence. Perhaps the most glaring gaps were related to the extent of the burden of fungal infections, both the fatal and non-fatal burdens. This is related to a number of challenges highlighted by the previous speakers. David spoke about the nature of fungal infections being common, yet not identified and picked and diagnosed in clinical practice, because often they are co-infections or misdiagnosed or missed altogether. A lot of the patients are immunocompromised, and in many countries, the patient that passes, that case is never closed in the clinical terminology, as in the definitive cause of death, the definitive diagnosis, in a lot of settings is not identified. That makes it hard to really gauge the burden of fungal infections.

There are a number of other factors also that contribute to the complexity of this burden. There are challenges that are highlighted by Ana, for example, in terms of the One Health aspect and the use of antifungals in the environment. This is the tip of the iceberg, the evidence that we have now, and I think more evidence is emerging and needed. There is more evidence needed to also understand the role of global warming in terms of impacting the distribution of some of these fungal infections, the severity of them, as well as the overall ecology of these pathogens.

There are a number of issues there that need to be addressed and we were hoping through this report to highlight the importance of these deadly pathogens, this largely neglected area. The goal here is to draw the focus and drive hopefully investments into research, basic research, also innovation and research and development of new treatments, expansion of access to existing treatments and diagnostics in an affordable fashion and David highlighted the importance of access in many countries. Major centers don't have access to basic mycology diagnostics, as well as even the limited number of classes of antifungals.

One more area that we are hoping through this report and the upcoming work that we will be doing is to also drive some investments into the research and development of new different models and optimization of existing treatments. Also, David touched on the need for optimized treatment and more effective treatments and diagnostics. Again, antifungal resistance is an area that also needs a lot of attention and a lot of work.

The speakers before also touched on this idea of funding. Here funding is a major challenge as it is for research and development of all infectious diseases. The area just in general is not attractive to investors. And that creates a need for the collective to address this through public funding. We, through our work, are trying to raise the profile of fungal infections, and especially the resistant fungal infections, and to include it in the discussions in different forums that focus on the prevention and control of antimicrobial resistance globally. We believe that eventually the solution to these, for lack of better term, broken market dynamics is for governments and member states to allocate funds to improve governance and commitment to address these important areas.

Lastly, I want to just touch also on the importance of public health interventions. And that includes also the importance of education and integration of this area of work into curriculum to medical training. Our

colleagues who have been doing this for a long time and who have traveled and assessed situations in different countries tell us that there are glaring gaps in the trainings, in the knowledge, which leads to also a lot of these infections being undiagnosed and leads eventually to a lot of patients suffering and unnecessary deaths and costs also in terms of the economic burden.

Erta Kalanxhi
41:50
Thank you, Hatim, for these really important points. These are great recommendations. But considering the epidemiology of the disease worldwide, as well as the fact that different countries have progressed at different stages to implement or address these issues, what would be the recommendations for countries to adopt these global guidelines at the national level?

Hatim Sati
42:23
I wouldn't first characterize the report recommendations as guidelines just yet. This is the next step of work to be done. We have been in deliberations and we have plans to have a stepwise approach at all three levels of the organization to address this issue in a coordinated fashion, as we do with many disease areas. Some, of course, will need to be addressed at the global level.

At the regional and the national levels, we are in close coordination with our colleagues in the surveillance teams, as well as our colleagues who are focused on what we call the global diagnostics initiatives. These are two areas that aim at strengthening and building capacity in the country for surveillance of disease and AMR, including fungal diseases, and also focused on ensuring access to quality diagnostics where it's needed, specifically to inform patient care.

The approach is, of course, being taken in a patient-centered fashion. As David earlier mentioned, to treat a patient you need the knowledge to have the diagnostic suspicion, you need a diagnostic tool, but also you need access to affordable care and treatment to treat your patient. So we're working in coordination with relevant teams in the essential medicines list and in the essential diagnostics list, specifically, the discussion around what it means for a drug to be in the essential medicines list or a diagnostic test to be an essential diagnostic test. And that is what David again touched on when he said, these drugs and the diagnostic tools and these lists need to inform procurement and financing should be put behind these procurement schemes to ensure steady supply. Of course, globally, there are a number of global issues around supply chain and drug production. That is a whole area of discussion. But all of these areas are challenges that need to be addressed and I must say, it feels like it's moving, but I think it should move faster. We are determined actually to keep on pushing on this topic in collaboration with, of course, partners and colleagues who are focused in this area.

Erta Kalanxhi
45:47
Thank you so much. I think we have a bit of time to address or answer some of the questions, I see that some of them have already been answered in the chat. A question open to perhaps, perhaps Dr.

Denning, or anybody else in the group. So one of the questions is about vaccination. Briefly, is there a perspective for vaccination, especially for candidiasis, which is the most common and invasive fungal infection?

David Denning
46:22
No, is the answer to that. There isn't. There aren't any fungal vaccines, there's the technical possibility of doing one for pneumocystis. But there wasn't an economic case that was possible. Aspergillosis is more complex, because you've got invasive, chronic, and allergic disease. So you're going to get those different types of disease sorted out.

There was a vaccine developed for *Candida* and it was trialed in women with recurrent vaginal candidiasis, and it was partially effective. But then it wasn't taken further. One of the difficulties with candidiasis is knowing who to vaccinate ahead of time. You may know that about a transplanted leukemic patient, but many of the patients who arrived in ICU, or have dialysis or renal failure, are not known ahead of time or don't respond very well to vaccines. Dialysis patients respond poorly to vaccines in general, for example. So the answer is, there isn't a vaccination strategy for the world at the moment. And there are no companies that I know of any size that are working on it.

Erta Kalanxhi
47:28
Thank you. I also see a few questions that have been answered in the [chat]. So I'd ask, for example, the question about the difficulties of developing antifungal drugs and vaccines to refer to the chat because there are some very good links there. But when it comes to antifungal resistance, and maybe a very quick answer from you, many people when they think about antimicrobial resistance, they sort of associate it with antibiotic resistance. Now, we're talking about antimicrobial resistance, which also includes antifungal resistance. And these two may be different. If they are, could you just elaborate a bit? How does antifungal resistance differ from antibacterial resistance? I don't think many are aware of this difference.

Ana Alastruey Izquierdo
48:16
Thank you. Yes, I think it's important. One of my main goals in the last month in all the meetings that I've been [in] is saying, whenever somebody says antibiotic resistance, I say antimicrobial, antimicrobial, because I think we have to use the the momentum and to use all the advocacy that all the people from antibacterial resistance have done highlighting the importance of this fact to use it for antifungals.

As I was saying, we are not in the same stage in a way that antifungal resistance is not as high as it is with bacteria. And one of the things that is influencing that is that, first, systemic antifungals are not usually sold over the counter as frequently as antibiotics. You use antifungals to treat nail and cutaneous infections, but that could be a problem in some places and we know from India that they are also over the counter. But one of the main differences with antibiotic and antifungal resistance is that, as far as I

know and up to now, there is no horizontal gene transfer in fungi. In bacteria, you can have a bacteria in your body that has a resistance mechanism and that, through a plasmid, can be transmitted to other bacteria. This is the horizontal transfer of genes that are resistant. In fungi, this is not such a big problem yet, because the fungal genomes are more complex and have a different way of developing resistance. Resistance usually happens through the continuous pressure on a specific strain or a species.

But we also have another point in fungal infections, which is that there are emerging species that are intrinsically resistant. That means that, as we were saying, all these species that are included in the priority list are intrinsically resistant to all antifungals. One of the things that I think is important too, when we compare antibacterials and antifungals is that, despite saying that we have a very limited number of antibacterial drugs in the pipeline, that they are not in development, in antifungals, it is really ridiculous. So we have mainly nine, ten different antifungal drugs, and in the pipeline, there are four or five, much better than in the previous decades. But it's still not enough, because we have some things that are not covered with the current situation. So in a way, we need to be aware that, although [antifungal resistance] is not such a big problem as it is with with antibacterial [resistance], we are [at a] point in which we can act, and we need to do surveillance, we need to investigate the research and do research in the mechanisms and the drivers of antifungal resistance, we need to understand a lot. We are far behind antibiotic resistance. And that's why I think we should use the antimicrobial world to be able to cover that.

Erta Kalanxhi
51:42
That's a very, very good point because despite the lower risk for acquiring resistance from horizontal transfer, when you talk about fungal infections, they take longer to treat or are more complicated to treat than most bacterial infections. And then you have also previously mentioned clinical resistance, so that comes from all these challenges.

Ana Alastruey Izquierdo
52:06
Erta, there are two points there. One is that, whenever we [consider] fungal infections, it's always after discarding bacterial and viral infections, so it's usually already delayed. That's one point which makes it difficult to treat the patient. And the second [point], we don't have really good antifungals. As David was saying, even if this strain is susceptible and you get levels of antifungal infection, mortality is still high sometimes. So we really need to do better.

Erta Kalanxhi
52:40
Thank you. I'm picking up a question that perhaps could benefit everybody here. A question from Justice Danso: are there platforms that focus on education and training, clinical or research personnel on diagnosis and identifying infections? Do such platforms exist?

David Denning

53:02
I think, to my knowledge, there isn't a specific sort of research training program per se, but there are loads of resources. The Mycoses Study Group runs webinars. The Asia Fungal Working Group runs webinars, ISHAM runs webinars. There are multiple congresses held in this area. We run the Life Fungal Education online which has got a lot of videos attached to it, which include how to do specific tests in the lab. There are other major resources, The Aspergillus Website, the ISHAM website is very informative, the Gaffi website's got a lot of information on it. So there are lots and lots of resources, but a lot of that is self learning, rather than being taught in a format, if I would put it that way.

Erta Kalanxhi
53:58
One final question, I believe it's for Dr. Denning. What would be the most cost effective tool for diagnosis of fungal infections?

David Denning
54:09
If you have a positive microscopy, then you've got excellent evidence of infection. But you have to have the right sample and many patients, particularly respiratory infection [patients], don't ever produce the sample so you can't do it. And it's insensitive, so you'll only pick up depending on what the topic area is: 20%, 50%, maybe for cryptococcal meningitis, 80%. It depends on the thing, but it's never 100%. So it's cheap, [but] it does require some skill. In broad cost effective terms, microscopy is absolutely core to any mycology laboratory.

Fungal culture is inexpensive, but it's also not very sensitive. So for aspergillosis it's about 30% sensitive, candidemia or invasive *Candidiasis* is about 40% sensitive. So you've got insensitivity of culture, but culture is really important because you can define exactly what the fungus is and you can do a susceptibility test.

The best test is probably cryptococcal antigen, but of course, cryptococcal disease is not that common. So if you're working in Belgium or in the Netherlands, you can do loads and loads of tests and none of them are ever positive, because the disease is so rare. The cost effectiveness depends on the frequency of the disease underlying it, and that therefore will vary by the different clinical settings in which you test. And there isn't a single test, it does require multiple tests, and it also requires being able to take the right sample bronchoscopy or corneal scraping or a lumbar puncture. It also requires radiology as well, and particularly for pulmonary sinus brain infections, you can't do that without radiology of some sort.

So it isn't always but it can be a complex area of medicine and people do need good training. But the answer to the question is no, there is not one single test that does it all.

Erta Kalanxhi
56:18

Thank you so much. And with that answer, we are just one minute over the hour. Thank you very much for joining today. We'll close the webinar for today. But I see that there are some comments about adding access to the links and some of the materials that we've shared here in the chat. If you'd like to have a list, please contact us at the email that came with the invitation. I'd like to thank our speakers today for taking the time and devoting their time to such an important topic, and we look forward to future webinars and more activities that bring awareness to fungal infections. Thank you everyone for joining and have a great day.