

Detection of Antifungal-Resistant *Trichophyton* Strain in France

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

[Sarah Gregory] Hello, I'm Sarah Gregory, and today I'm talking with Dr. Karen Wu, an EIS officer at CDC in Atlanta. We'll be discussing the detection of an antifungal-resistant *Trichophyton* strain in France.

Welcome, Dr. Wu.

[Karen Wu] It's great to be here.

[Sarah Gregory] Dr. Wu is actually discussing two articles that she's not an author on, I just want to make that clear right now. But she is an expert in this field.

So first off, what is *Trichophyton*?

[Karen Wu] *Trichophyton* is actually a genus of fungi that causes dermatophytosis. Most people know this as ringworm, and this causes dermatophytosis in both people and animals. It's actually a mold that feeds on the keratin in nails, hair, and skin.

[Sarah Gregory] What is *T. mentagrophytes* complex?

[Karen Wu] So this classification of dermatophyte species is actually quite complex and has changed in recent years. *Trichophyton mentagrophytes* complex includes several different species and genotypes that are actually pretty difficult to differentiate just by looking under the microscope. This complex includes things like *Trichophyton mentagrophytes* (of course), *Trichophyton interdigitale* and *erinacei*. These species can only be differentiated using DNA sequencing. And also, within this complex, there are zoophilic strains, which means that they prefer animals (such as *Trichophyton mentagrophytes* and *erinacei*). And there's also anthropophilic strains, which means that they prefer people (such as *Trichophyton interdigitale*).

[Sarah Gregory] And speaking of people, in what ways does it affect people?

[Karen Wu] So dermatophytosis can cause an itchy, scaly, ring-shaped rash, which is why people know it as ringworm. And the names of these clinical manifestations depend on the body site that's affected. For example, if the body.... if the infection is on the body, it's known as tinea corporis; if it's on the groin, it's known as tinea cruris. Tinea capitis is infection of the scalp, and tinea faciei is actually infection of the face. It can also cause infections we all recognize such as Athlete's Foot or tinea pedis, and fungal nail infections, also known as onychomycosis or tinea unguium.

[Sarah Gregory] Is it spread from person to person? And if so, how does that happen?

[Karen Wu] Yes, it does. Anthropophilic strains of dermatophytes can be spread from person to person by direct contact or through contact with contaminated surfaces or shared articles of clothing. This can include towels, bedding, or shoes, and transmission can easily occur in areas like households, gyms, and schools or daycares where people have a lot of contact with each other. Zoophilic strains can be transmitted from animal-to-animal but can also infect people. People-to-animal transmission is rare but is still suspected to be possible.

[Sarah Gregory] How is it usually treated?

[Karen Wu] It really depends on the body site affected and the severity of the infection. But ringworm can be treated using topical or oral antifungal medications such as terbinafine, itraconazole, or fluconazole.

[Sarah Gregory] Can this cause long-term damage to the skin if it goes untreated?

[Karen Wu] So people who are infected can get secondary bacterial infections of the affected area since this is an itchy condition, and so scratching can disrupt the skin's surface and introduce bacteria. Topical corticosteroid use can also lead to abnormal presentations that can mimic other skin conditions such as eczema, psoriasis, or dermatitis, and this called, "steroid-modified tinea". This fungi can also spread deeper into the skin and into the subcutaneous tissues and hair follicles, and this actually leads to a presentation called Majocchi's granuloma. A patient also would not want this to go untreated. This condition is very, very itchy, and so it's pretty uncomfortable. And so prompt treatment is really important to maintain a person's quality of life.

[Sarah Gregory] EID published two articles about a new strain of antifungal resistant *Trichophyton* species in France. Where was it first identified and how did it get into France?

[Karen Wu] So about 10 years ago, we started seeing reports from dermatologists from India, and they started publishing articles on cases of chronic and recurrent dermatophytosis. And we didn't really know what was going on or what was causing this change in presentation. It was soon discovered that it was part of, actually, the *Trichophyton mentagrophytes complex*, but limitations in laboratory testing and sequencing really hindered the identification of *Trichophyton indotineae* until about 2020. So the first case of *Trichophyton indotineae* in France was observed in 2017 and was laboratory-confirmed to be *Trichophyton indotineae* retrospectively. All of the cases described in these articles came from or visited the Indian subcontinent.

[Sarah Gregory] So is it endemic to a certain country or region?

[Karen Wu] So it's currently known to be endemic on the Indian subcontinent and in Iran, although additional cases have been identified in Australia, Germany, Denmark, Poland, Belgium, Switzerland, and of course, France. It is likely in other areas, but again, detecting *Trichophyton indotineae* is really difficult because clinical laboratories rarely identify dermatophyte mold to the species level.

[Sarah Gregory] Do environmental factors play any kind of role in its spread?

[Karen Wu] Yeah, yes it does. So dermatophytes in general prefer warm areas with high humidity, both on people and in the environment. People exposed to hot and humid environments, overcrowding, or people who wear tight-fitting synthetic clothing are at higher risk. Cases of *Trichophyton indotineae* often seem to occur among family members, which can be due to a common exposure to a shared contaminated environment or increased direct contact among family members. It is also made worse by the use of over-the-counter medications that include antifungals and high-potency steroids.

[Sarah Gregory] Did you say, "made worse" by those?

[Karen Wu] Yes, yes, it is.

[Sarah Gregory] How does that happen?

[Karen Wu] Actually, the problem is that these antifungals are combined with high-potency steroids. And the steroids, although they resolve the itching, do not resolve the antifungal or do not resolve the infection.

[Sarah Gregory] Ah, I see. Were there many people affected in France?

[Karen Wu] So these two studies described 17 people with difficult-to-treat or extensive dermatophytosis in France. About 14 cases were identified as *Trichophyton indotineae*, and the species was not actually identified for three cases. Given the challenges of diagnosis (and that's even highlighted in these two studies, since the species was not able to be identified for three of these cases), it is very likely that there are additional cases in France.

[Sarah Gregory] But some of them were able to be diagnosed. How was that done?

[Karen Wu] So these cases were initially diagnosed as dermatophytosis using physical exam or microscopy. Some patients...these patients in these studies had abnormal presentations. They had very extensive presentations or were associated with treatment failure, and so the researchers focused on laboratory testing. They were able to identify *Trichophyton indotineae* by sequencing the ribosomal DNA, and then they were able to determine that this strain was resistant to antifungal drugs by conducting susceptibility testing of the isolate combined with DNA sequencing to identify gene mutations for drug resistance.

[Sarah Gregory] And I know you just touched on this a while ago, but do we know how any of these people got infected? What was the source?

[Karen Wu] So many of the reported cases in France occurred in people with recent travel to the Indian subcontinent. So we think that people have been getting infected from direct contact with infected people. So this is very common in households. Transmission in family members has been very, very commonly noted in the literature.

[Sarah Gregory] Are there particular animals that serve as a reservoir for this strain?

[Karen Wu] So terbinafine-resistant *Trichophyton mentagrophytes* has been detected in asymptomatic foxes in Poland and in people with dermatophytosis associated with animal transmission, and these are usually associated with things like guinea pigs and chinchillas. *Trichophyton mentagrophytes* complex includes *Trichophyton indotineae*, but due to previously mentioned laboratory limitations, these strains were not definitively classified as *Trichophyton indotineae*.

[Sarah Gregory] So guinea pigs and chinchillas can be household pets, so people might want to be aware of that. But we're not seeing it in dogs or cats?

[Karen Wu] There haven't been any reported cases thus far that I'm aware of in dogs or cats.

[Sarah Gregory] Do you know of, or from these studies, has it shown that there's been any person-to-person transmission of it in France?

[Karen Wu] So although *Trichophyton mentagrophytes* has historically been considered zoophilic, it's actually primarily happening through people-to-people contact. Three reported cases involved skin lesions that appeared after living in France for three to four years, so researchers think that person-to-person transmission could have occurred in France. None of these patients had notable contact with animals.

[Sarah Gregory] What about the rest of Europe? Has it been seen in other European countries?

[Karen Wu] So *Trichophyton indotineae* has been identified in other European countries such as Germany, Denmark, Poland, Belgium, and Switzerland. Similar to France, many of these reported cases were associated with either recent travel to the Indian subcontinent or were family of an individual with recent travel.

[Sarah Gregory] How about the US?

[Karen Wu] So in the United States, there has been one case report thus far of a case of *Trichophyton mentagrophytes* associated with terbinafine resistance. It was unfortunately unable to be laboratory-confirmed as *Trichophyton indotineae*.

[Sarah Gregory] This new strain is resistant to the antifungal medication terbinafine, which is the preferred first-line treatment. How did this resistance happen?

[Karen Wu] So in India, researchers suspect that the rise of this strain is connected with the use of high-potency steroid creams, such as clobetasol. It's commonly combined with antifungal medications to treat dermatophytosis. These creams don't need a prescription and are sold over the counter in pharmacies in other countries, and these steroids might resolve the itching but do not treat the underlying fungal infections and can actually stimulate fungal growth. Once these symptoms resolve, patients will sometimes stop using antifungal medication, and this can lead to incomplete treatment and potentially selecting for resistance.

[Sarah Gregory] Like so much of antibiotic use. So we're seeing it now with antifungal use.

Is this resistance a cause of concern? I would think it would be.

[Karen Wu] It certainly is. Only a limited number of antifungal drugs are available, and treatment of fungal diseases can be lengthy and difficult. Also, antifungal medications are actually quite expensive, and a long course of medications can be cost prohibitive. Some of these infections are also multidrug resistant, and dermatologists are reporting difficulties in treating this condition.

[Sarah Gregory] You've mentioned several strains now, but particularly we're talking about a new strain. Can you tell us again which one that is and how it's different compared to other strains?

[Karen Wu] Yeah. So the primary one that is causing issues is *Trichophyton indotineae*. So in addition to its problematic drug resistance, this strain is a little more virulent, like zoophilic strains. And so these are just a little bit more inflammatory, more itchy, but is also spread from people-to-people like anthropophilic strains. The presentation of this disease is also slightly different. Tinea corporis and tinea cruris—and just as a reminder, that's infection of the body and also the genital area—are the two most common presentations. Multiple body sites are often involved, with extensive lesions that cover a large area of the body, which we are defining as more than 10%.

[Sarah Gregory] Are there other options for treating it other than these antifungals that aren't working?

[Karen Wu] So there's not an option that isn't an antifungal. There is an antifungal medication (itraconazole) that is currently the treatment of choice for terbinafine-resistant dermatophytosis. But it still has high rates of treatment failure. Griseofulvin and fluconazole can also be prescribed but are not preferred.

[Sarah Gregory] What happens when there's treatment failure?

[Karen Wu] So it's up to the dermatologist, but sometimes they can increase the dosage or the length of time someone is administered an antifungal, or they can switch to a different antifungal.

[Sarah Gregory] How can we stop this infection from spreading? Is there a way?

[Karen Wu] So first, you can definitely take steps to prevent dermatophytosis; don't walk barefoot in areas like locker rooms or public showers, don't share clothing, sheets, or towels with individuals who may be infected, and keep your skin clean and dry. Clinicians should be aware of the rise of treatment-resistant dermatophytosis, and patients presenting with potential dermatophytosis lesions should receive confirmatory laboratory testing prior to being prescribed these antifungal medications. Molecular testing and antifungal susceptibility testing should be done as indicated.

Because this fungus is drug resistant, antifungal stewardship is really now just so important. Timely and proper antifungal medication administration is just so important to controlling further infections, and patients should really be counseled on the importance of proper antifungal usage and taking a prescription exactly as directed by the physician.

[Sarah Gregory] So these are the best ways to prevent more antifungal-resistant strains?

[Karen Wu] Yes. In addition to improved antimicrobial stewardship, we aim to decrease and discourage the use of over-the-counter combination drugs, which is these antifungal medications combined with high-potency topical steroids. These medications are currently available overseas and are commonly recommended by various medical and non-medical professionals.

[Sarah Gregory] What are the psychological effects on people who have this condition?

[Karen Wu] So a study measured the effect of this disease on the patient's quality of life, and its impact was estimated to be moderate to very large. The most important determinant of quality of life was really the symptoms of the skin—so itchiness, soreness, and pain. Other factors that they found included self-consciousness, restrictions on clothing, more limited social and leisure activities and limited interaction with others, as well as treatment outcomes.

In general, these lesions are very itchy and can cover large portions of the body, with over 80% of patients having lesions that cover more than 10% of their body. Patients have reported being infected for months and even years. And, of course, treatment failures can occur.

[Sarah Gregory] What points of these articles do you think have the most public health significance?

[Karen Wu] I think one of the most important concerns with this disease is actually the difficulty in diagnosis. Molecular testing for these...for cases of dermatophytosis is not commonplace in laboratories, and clinicians don't normally order antifungal susceptibility testing. Without this testing, a case of terbinafine-resistant *Trichophyton indotineae* would remain undiagnosed and the patient would be treated with potentially ineffective antifungal medications.

[Sarah Gregory] You're a veterinarian by training and, currently, an EIS officer at CDC. Tell us why you came to CDC and how you became interested in this topic. As I said earlier, you're not one of the coauthors, so how are you involved in studying *Trichophyton*?

[Karen Wu] So actually, before I became a veterinarian, I knew I wanted to go into public health, and where better than the CDC? I enjoy working on diseases from a One Health perspective, and the Mycotic Diseases Branch has provided plenty of opportunities. I've had the chance to work on diseases affecting animals and people such as blastomycosis, sporotrichosis, and of course, dermatophytosis. I saw many cases of animal-to-animal and animal-to-people transmission during my veterinary work in the United States. But thankfully, my animal cases were not drug resistant.

As for my current work, we're currently trying to learn more about treatment-resistant *Trichophyton* in the United States. Two case reports have been published, one on *Trichophyton rubrum* and the other one on *Trichophyton mentagrophytes*. Since of course the United States is not an island, we are concerned that these cases will actually continue to be imported and may lead to transmission within the United States.

We're also working on onychomycosis (or tinea unguium), which is a dermatophytosis infection of the nail. It is closely associated with tinea pedis (which is the dermatophyte infection of the foot). And similar challenges have arisen, including the emergence of drug-resistant onychomycosis in the United States. Although there are guidelines to confirm diagnosis of onychomycosis prior to antifungal prescription, we have found that this does not always occur.

[Sarah Gregory] And what is that a fungus of?

[Karen Wu] That is a fungal infection of nails.

[Sarah Gregory] The nails, okay.

What are some of your favorite activities that you enjoy doing in Atlanta? It's spring here, which is particularly pretty in Atlanta but also incredibly polleny. There's a green coating that settles on everything. Does that affect you?

[Karen Wu] So I really enjoy hiking and playing board games and visiting restaurants. So of course outdoor activities are now covered in this green that you mentioned. Just recently, the weather has been quite lovely, and it has been great outside. Unfortunately, I am allergic to pollen, and so this has been limiting a little bit of my outdoor activity. But definitely masking has improved things.

[Sarah Gregory] Yes, I wear the mask even in my own backyard because of it.

Well, thank you for taking the time to talk with me today, Dr. Wu.

[Karen Wu] Thank you so much for having me. It has been a pleasure.

[Sarah Gregory] And thanks for joining me out there. You can read the January 2022 articles, Extensive Dermatophytosis Caused by Terbinafine-Resistant *Trichophyton indotineae*, France, and Emergence of Difficult-to-Treat Tinea Corporis Caused by *Trichophyton mentagrophytes* Complex Isolates, Paris, France, online at [cdc.gov/eid](https://www.cdc.gov/eid).

I'm Sarah Gregory for *Emerging Infectious Diseases*.

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