# Clinical alert: arrival of terbinafine resistant Trichophyton indotineae in New Zealand

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## ABSTRACT

**BACKGROUND:** Over the past decade there has been a rapid emergence of a new dermatophyte species *Trichophyton indotineae* (*T. indotineae*) in the Indian subcontinent, with associated global spread. It is noted for extensive recalcitrant infections and high rates of terbinafine resistance that are changing treatment paradigms for tinea infection.

**AIM:** To report on the epidemiology of dermatophyte infections from the National Mycology Reference Laboratory at Auckland City Hospital and the arrival of *T. indotineae* in New Zealand.

**METHODS:** This was a retrospective review of laboratory data from January 2017 to August 2024. Antifungal susceptibility was performed by disc testing. Species identification was performed by phenotypic methods and for a limited number of isolates by DNA sequence analysis.

**RESULTS:** There were 961 dermatophytes identified. *Trichophyton rubrum* was the most common species, accounting for 72% of all isolates. There were 85 (9%) confirmed or probable *T. indotineae* identified from 63 individuals. These included both Auckland isolates and isolates referred from laboratories around the country. Of the 49 *T. indotineae* isolates that had antifungal susceptibility testing performed, only 30 (61%) were susceptible to terbinafine, while 45 (92%) were susceptible to itraconazole.

**CONCLUSIONS:** Terbinafine resistant *T. indotineae* has arrived in New Zealand. To assist appropriate management, practitioners encountering extensive tinea infection, particularly if failing terbinafine treatment, should request culture, asking for full dermatophyte identification and susceptibility testing. Itraconazole is the recommended treatment for *T. indotineae*, and up to 12 weeks duration may be required.


Dermatophytosis is one of the most common fungal infections worldwide.[1] It is caused by a group of keratinolytic filamentous fungi known as dermatophytes that infect superficial tissues such as the stratum corneum, hair and nails.[1] Anthropophilic and zoophilic species in the genera *Trichophyton*, *Epidermophyton* and *Microsporum* are responsible for most infections.[1,2]

Dermatophyte epidemiology displays significant geographic and temporal variation.[1,2] Epidemiological changes have included the emergence of *Trichophyton rubrum* (*T. rubrum*) as a globally widespread pathogen associated with tinea pedis and onychomycosis in the 1940–1950s. Similarly, *Trichophyton tonsurans* (*T. tonsurans*) replaced *Microsporum canis* (*M. canis*) as the dominant cause of tinea capitis in the United Kingdom at the end of the twentieth century.[1–3] Over the past decade, *Trichophyton indotineae* (*T. indotineae*) (previously called *Trichophyton mentagrophytes* genotype VIII) has replaced *T. rubrum* in India in association with an epidemic of tinea corporis/cruris.[4–6] *T. indotineae* is now also being isolated in regions outside the Indian subcontinent.[7–9] In New Zealand, *T. rubrum* was the most common species reported in two studies from Wellington (1975–1979) and Auckland (1999–2002).[10,11]

Antifungal resistance has not historically been a concern in the treatment of dermatophytes. However, this paradigm is shifting, with increasing reports of resistance to the first line anti-dermatophyte agent terbinafine. Most notable has been the emergence of *T. indotineae* associated with recalcitrant infections and high rates of terbinafine resistance (up to 71%).[12–15] A proportion of these isolates also have decreased susceptibility to the triazoles.[15] Terbinafine resistance has also been observed less frequently in *T. rubrum*.[13,15] Treatment-resistant *T. indotineae* has recently been reported in Australia, but there are no published data on its presence in New Zealand.[16]

We have examined the laboratory data from the National Mycology Reference Laboratory at Auckland City Hospital with the aims of reporting on the current epidemiology of dermatophyte infections and the arrival of *T. indotineae* in New Zealand.

## Methods

We searched our laboratory information system for the period January 2017 to August 2024 to identify dermatophyte positive specimens and referred isolates from other New Zealand laboratories. For each isolate we extracted data on the specimen site, location of referring laboratory and susceptibility results. Dermatophytes were primarily identified by standard microscopic and macroscopic characteristics. Since 2017, we have encountered atypical strains of *Trichophyton interdigitale* (*T. interdigitale*) that were urease negative (*T. interdigitale* is urease positive) and that had abundant macroconidia (none or sparse for *T. interdigitale*). We have reported these as "atypical *T. interdigitale*". If these were speciated by molecular methods, we reported as *T. indotineae*. For this report we refer to the isolates as *T. indotineae*/probable *T. indotineae* based either on DNA sequencing or the atypical morphology described above. Molecular identification was performed on two isolates, one resistant and one with intermediate terbinafine susceptibility. The isolates' internal transcribed spacer (ITS) region was amplified using PCR Buffer and Taq DNA polymerase. The amplified products were sequenced twice in both directions (forwards and reverse). The sequences were then compared to the ITS sequences of all fungal isolate accessions in the National Center for Biotechnology Information GenBank database.

Susceptibility testing is not performed routinely on dermatophytes; however, requests have been increasing in recent years associated primarily with dermatologists managing recalcitrant infections. Disc diffusion antifungal susceptibility testing (AFST) is performed locally for dermatophytes following the disc manufacturer methods.[17] Briefly, the isolates are sub-cultured at 30 degrees Celsius for 4–15 days (until sporulation confirmed); the inoculum (conidial suspension) is then prepared in sterile saline, adjusted to a 0.5 McFarland standard and inoculated onto Mueller–Hinton agar with 2% glucose and 0.5μg/mL methylene blue. Antifungal discs (Neo-Sensitabs™, Rosco Diagnostica A/S, Taastrup, Denmark) are placed onto the inoculated agar. These discs include terbinafine (30μg), fluconazole (25μg), itraconazole (10μg) and voriconazole (1μg). Plates are incubated at 30 degrees Celsius in ambient air with reading on day 4 (and up to 7 days for slow growing organisms). Interpretive criteria recommended by the manufacturer for local (topical) treatment of *Candida* species are used; for fluconazole and terbinafine, susceptible, intermediate and resistant zone sizes are ≥20mm, 12–19mm and ≤11mm respectively. For itraconazole, the zone sizes are ≥15mm, 10–14mm and no zone.[18] The manufacturer has no recommendation for voriconazole, and the fluconazole zone sizes are used.

## Results

From January 2017 to August 2024, we isolated or identified 961 dermatophytes (Table 1). *T. rubrum* was the most common isolate (688, 72%) and was the most frequent species from all body sites except the scalp. Scalp infections were mostly caused by the well-recognised causes of tinea capitis, *M. canis* and *T. tonsurans* (Table 2). Feet and nails (mostly toenails) were the most common sites of infection (Table 2).

Since 2017 we have identified 85, molecularly confirmed (2) or probable (83), *T. indotineae* isolates. These included 24 from our own specimens, 22 from the local community laboratory, 17 from other Auckland hospital laboratories and 22 referred isolates from laboratories outside Auckland. From 2021 there have been more confirmed or probable *T. indotineae* than *T. interdigitale* identified (Table 1). The 85 *T. indotineae* isolates were from 63 patients, 50 with one isolate, seven with two, four with three, one with four and one with five isolates. The most common sites of infection were groin 28%, thighs 13%, feet 12% and arms 12% (Table 2). The median time between isolates for the six patients with cultures separated in time was 6 months, ranging from 1 to 18 months.

Available antifungal susceptibility results for 49 confirmed or probable *T. indotineae* and 24 *T. rubrum* are summarised in Table 3. Itraconazole was the most active agent, with 92% and 100% of *T. indotineae* and *T. rubrum* isolates testing susceptible respectively. For terbinafine only 61% and 92% of *T. indotineae* and *T. rubrum* tested susceptible respectively. Fluconazole was the least active agent (Table 3). All terbinafine resistant isolates had no zone of inhibition around the discs. It was also notable that there was a difference in the disc zone sizes for terbinafine susceptible strains of *T. rubrum* and *T. indotineae*: 21 of the 22 (95%) susceptible *T. rubrum* isolates had zone sizes ≥40mm, whereas only 19 of the 30 (63%) susceptible *T. indotineae* had zone sizes ≥40mm.

## Discussion

Our laboratory data show that the local epidemiology of the common dermatophytes is similar to past reports, with *T. rubrum* the most common species at all sites except the scalp.[11] The notable exception is the emergence of *T. indotineae* that made up 9% of isolates. This, however, is likely a much higher proportion than an unbiased community sample, due to the reference laboratory's selective receipt of isolates from recalcitrant infections for antifungal susceptibility testing. Of the *T. indotineae* isolates, only 61% were terbinafine susceptible. Consistent with prior reports, a greater proportion, including terbinafine resistant isolates, were susceptible to itraconazole.[9,12] This local emergence of terbinafine resistant *T. indotineae* threatens to complicate tinea treatment locally, as it is doing in many areas globally.

There are limitations to the data, including the formal molecular identification of only two *T. indotineae* isolates, although the phenotype features, and resistance, of the probable *T. indotineae* isolates make their identity highly likely. Another limitation is that we did not use a standardised technique to determine antifungal minimum inhibitory concentrations (MICs), preventing in-depth comparisons with other susceptibility reports. However, others have shown that disc testing methodology (using different antifungal concentrations than locally) for dermatophytes generates reproducible zone diameters, and zone sizes correlate to MICs.[19–21] It is likely the utilised zone diameter cut-offs to define susceptibility in this report are suboptimal, and the difference observed for susceptible *T. indotineae* versus *T. rubrum* isolates suggests we may be underestimating terbinafine resistance. Our finding that terbinafine resistant isolates were susceptible to itraconazole is consistent with sizeable studies reporting on *T. indotineae* isolates for which the terbinafine MICs were elevated (>2mg/L and many >32mg/L) having low itraconazole MICs (≤0.03mg/L).[9,12] As this was a laboratory-based study, we have no information on travel history, ethnicity, the extent of infection or response to treatment. Some patients did, however, have infection for some time, with positive cultures separated by up to 18 months.

We are planning a more in-depth analysis on our isolates using molecular methods to confirm species identity, detect squalene epoxidase (SQLE) mutations known to confer resistance to terbinafine and perform MIC measurements. This testing will allow better determination of isolates susceptibility and reveal how terbinafine disc zone sizes correlate to MICs and SQLE mutations.

In the meantime, however, we alert clinicians in primary care to be aware of the possibility of *T. indotineae* in persons with extensive long-standing tinea corporis and/or tinea cruris, particularly in those of Indian or other South Asian ethnicities that have failed terbinafine treatment. In this setting, we recommend that culture for dermatophytes is specifically requested of the local laboratory, and that if an atypical isolate is recovered that the initial laboratory refers the isolate for susceptibly testing and formal identification. Faced with a likely clinical history, it would be reasonable to initiate itraconazole treatment. The optimal dosing regimen and treatment duration have not been established, but 200–400mg daily for 2–12 weeks tailored to patient response (resolution of skin lesions) has been recommended.[7,8,22,23] The addition of a topical antifungal agent to systemic therapy may be considered; however, data are lacking on whether this improves therapeutic outcome.[8,23] The use of topical steroids should be avoided.

### Conclusions

Terbinafine resistant *T. indotineae* can be added to the list of antifungal resistant fungi, including *Candida auris* and azole-resistant *Aspergillus fumigatus*, which are now being encountered in New Zealand.[24,25] To enable appropriate management, practitioners encountering extensive tinea infection, particularly if failing terbinafine treatment, should request culture, asking for full dermatophyte identification and susceptibility testing. Itraconazole is the recommended treatment for *T. indotineae*, and up to 12 weeks duration may be required.

**Table 1:** Dermatophyte isolates January 2017–August 2024: Auckland City Hospital National Mycology Reference Laboratory.

| | Year of isolation | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Dermatophyte groups** | **2017** | **2018** | **2019** | **2020** | **2021** | **2022** | **2023** | **2024** | **Total** | |
| *Epidermophyton floccosum* | - | 3 | 2 | 1 | 2 | - | 2 | 1 | 11 | 1% |
| *Microsporum canis* | 4 | 2 | 3 | 5 | 2 | 1 | 2 | - | 19 | 2% |
| *Microsporum* other[1] | 1 | 1 | - | 1 | - | 1 | - | 2 | 6 | 0.6% |
| *Trichophyton indotineae*[2] | 8 | 1 | 6 | 10 | 24 | 14 | 10 | 12 | 85 | 9% |
| *Trichophyton interdigitale* | 21 | 23 | 12 | 14 | 6 | 9 | 10 | 5 | 100 | 11% |
| *Trichophyton* other[3] | 3 | 9 | 4 | 4 | 1 | 3 | 4 | - | 28 | 3% |
| *Trichophyton rubrum* | 80 | 112 | 81 | 107 | 106 | 67 | 72 | 63 | 688 | 72% |
| *Trichophyton tonsurans* | 2 | 4 | 7 | 1 | 3 | 4 | 1 | 2 | 24 | 2% |
| Total | 119 | 155 | 115 | 143 | 144 | 99 | 101 | 85 | 961 | 100% |

[1]Includes: *Lophophyton (Microsporum) cookei* (1), *Microsporum audouinii* (1) and *Nannizzia gypsea* (*Microsporum gypseum*) (4).
[2]Comprises two confirmed isolates identified by molecular sequencing and 83 probable isolates based on phenotypic characteristics.
[3]Includes: *Arthroderma insingulare* (*Trichophyton terrestre*) (3), *Trichophyton equinum* (1), *Trichophyton mentagrophytes* (7), *Trichophyton verrucosum* (2), *Trichophyton violaceum* (7) and *Trichophyton* species not further identified (8).

**Table 2:** Sites of dermatophyte infection for 961 isolates, January 2017–August 2024.

| | Site of dermatophyte infection | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Dermatophyte groups** | **Body** | **Groin** | **Foot** | **Nail** | **Scalp** | **Unknown** | **Total** | |
| *Epidermophyton floccosum* | 2 | 1 | 6 | 2 | - | - | 11 | 1% |
| *Microsporum canis* | 5 | - | 1 | - | 13 | - | 19 | 2% |
| *Microsporum* other[1] | 2 | - | - | 2 | 2 | - | 6 | 0.6% |
| *Trichophyton indotineae*[2] | 40[4] | 24 | 10 | 4 | - | 7 | 85 | 9% |
| *Trichophyton interdigitale* | 12 | 8 | 47 | 29 | - | 4 | 100 | 11% |
| *Trichophyton* other[3] | 13 | 1 | 1 | 3 | 9 | 1 | 28 | 3% |
| *Trichophyton rubrum* | 172 | 117 | 218 | 159 | 2 | 20 | 688 | 72% |
| *Trichophyton tonsurans* | 1 | - | - | - | 22 | 1 | 24 | 2% |
| Total | 247 | 151 | 283 | 199 | 48 | 33 | 961 | 100% |

[1]Includes: *Lophophyton* (*Microsporum*) *cookei* (1), *Microsporum audouinii* (1) and *Nannizzia gypsea* (*Microsporum gypseum*) (4).
[2]Comprises two formally identified by molecular sequencing and 83 probable isolates based on phenotypic characteristics.
[3]Includes: *Arthroderma insingulare* (*Trichophyton terrestre*) (3), *Trichophyton equinum* (1), *Trichophyton mentagrophytes* (7), *Trichophyton verrucosum* (2), *Trichophyton violaceum* (7) and *Trichophyton* species not further identified (8).
[4]Body sites were thigh (11), upper limb (10), chest/back (7), abdomen (5), face/neck (5) and leg (2).

**Table 3:** Antifungal susceptibility of *Trichophyton indotineae* and *Trichophyton rubrum*.[1]

| Organism | Terbinafine | | | Fluconazole | | | Itraconazole | | | Voriconazole | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | S | I | R | S | I | R | S | I | R | S | I | R |
| *Trichophyton indotineae* (N=49)[2] | 30 (61%) | 11 (22%)[3] | 8 (16%)[3] | 10 (21%) | 3 (7%) | 34 (72%) | 45 (92%) | 2 (4%) | 2 (4%) | 27 (73%) | 1 (3%) | 9 (24%) |
| *Trichophyton rubrum* (N=24) | 22 (92%) | 2 (8%)[4] | - | 17 (81%) | 2 (10%) | 2 (10%) | 24 (100%) | - | - | 17 (100%) | - | - |

[1]S = susceptible; I = intermediate; R = resistant. Disc susceptibility results.
[2]Comprises two formally identified by DNA sequencing and 47 probable isolates based on phenotypic characteristics.
[3]All isolates with intermediate susceptibility and seven (88%) of the eight terbinafine resistant isolates were susceptible to itraconazole.
[4]Both isolates susceptible to itraconazole.

**COMPETING INTERESTS**
Nil.

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