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UNEXPLORED HOST GENETIC AND SKIN MICROBIOTA FACTORS IN TINEA IMBRICATA: IMPLICATIONS FOR CLINICALLY PROVEN CURE STRATEGIES

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Abstract

Tinea imbricata (ringworm), a tropical fungal infection due to Trichophyton concentricum, is a neglected tropical disease prevalent in indigenous populations of Southeast Asia, Oceania, and Central and South America. Despite more than 50 years of reported endemicity, the reasons underlying its distinct geographical and ethnic distribution remain obscure. We bring together available evidence on host genetics and skin microbiota in tinea imbricata disease, highlighting two key yet underexplored factors. We discuss emerging information about antifungal drug resistance, including the recent identification of terbinafine resistant T. concentricum strains among indigenous Malaysian populations, as well as the latest treatment approaches, including new drugs in the pipeline. Literature was searched via PubMed, ScienceDirect and clinical trial registries up to June 2025. There is evidence for both autosomal dominant and recessive modes of inheritance with candidate genes such as DEFB4 (β-defensin 2) and CLEC7A (dectin-1) associated with susceptibility. Studies focusing on skin microbiome demonstrate decreased commensal bacteria (Cutibacterium acnes, Staphylococcus epidermidis) in populations, implicating microbiome dysbiosis in the development of this condition. Therapeutic outcomes are poor and relapse rates are more than 50% at six months. The growing reports of terbinafine resistance justify revisit to current antifungal algorithms. We advocate for a paradigm incorporating host genetic screening, microbiome and antifungal resistance for clinically cured tinea imbricata. Knowledge gaps include lack of genome-wide association studies, microbiome longitudinal studies and randomized trials in endemic countries.

1. Introduction

Tinea imbricata (or "Tokelau", and "bakua" in the Solomon Islands) is a highly distinctive and geographic disease among human fungal infections. This chronic superficial fungal disease (caused by anthropophilic dermatophyte Trichophyton concentricum) is characterized by scaling that occurs in concentric rings that take on the appearance of roof tiles, a pattern not seen in other dermatophytic infections. The condition was first reported by William Dampier in the Philippines in 1789 and it continues to be endemic among indigenous populations despite the impact of modernization on the surrounding population.

The distribution of tinea imbricata is highly endemic. The infection is endemic among indigenous populations of several countries

including Papua New Guinea, Solomon Islands (10-20% incidence), Malaysia (Orang Asli), Indonesia and remote populations of Mexico and Guatemala. What is especially interesting about this epidemiology is that as individuals from non-endemic areas are rarely affected when exposed, even after extensive personal contact, even with infected family members, suggesting inherent host factors at play.

The disease has far-reaching clinical implications. Patients endure persistent itching, secondary infection through scratching, and intense stigma and ostracism. Although there is antifungal treatment, over 50% of patients relapse within 6 months and access to treatment is limited in isolated endemic regions(Er et al., 2022).

The disease has entered a new chapter in 2015 following two key advances. First, the release of the first T. concentricum reference genomes from Malaysian Orang Asli patients has allowed molecular epidemiology monitoring and gene identification of resistance. Second, the first reports of terbinafine-resistant isolates with point mutations in the squalene epoxidase (SQLE) gene have highlighted an urgent need to determine the best treatment approaches. Finally, the first skin microbiome studies on affected populations have shown depletion of beneficial commensals (Cutibacterium acnes, Staphylococcus epidermidis), clearly indicating microbiome dysfunction as a heretofore unknown factor in disease pathogenesis(Ghosh & Panda, 2023).

Here we review the current evidence and highlight the two least studied areas in tinea imbricata, related to host genetics and microbiome contributions. By critically reviewing evidence for autosomal dominant and recessive patterns of inheritance, screening for candidate genes such as DEFB4 (β-defensin 2) and CLEC7A (dectin-1), and new data on antifungal resistance, we explore pathways toward clinically proven curative strategies that integrate host genetic screening, microbiome restoration and resistance-based antifungal selection in this neglected tropical disease. Our focus is to establish strategies for the delivery of clinically validated treatment for this neglected tropical disease through strategies combining host genetic screening, microbiome restoration and screening candidate antifungal compounds for resistance.nce; indigenous health(Gnat, Łagowski, & Nowakiewicz, 2021).

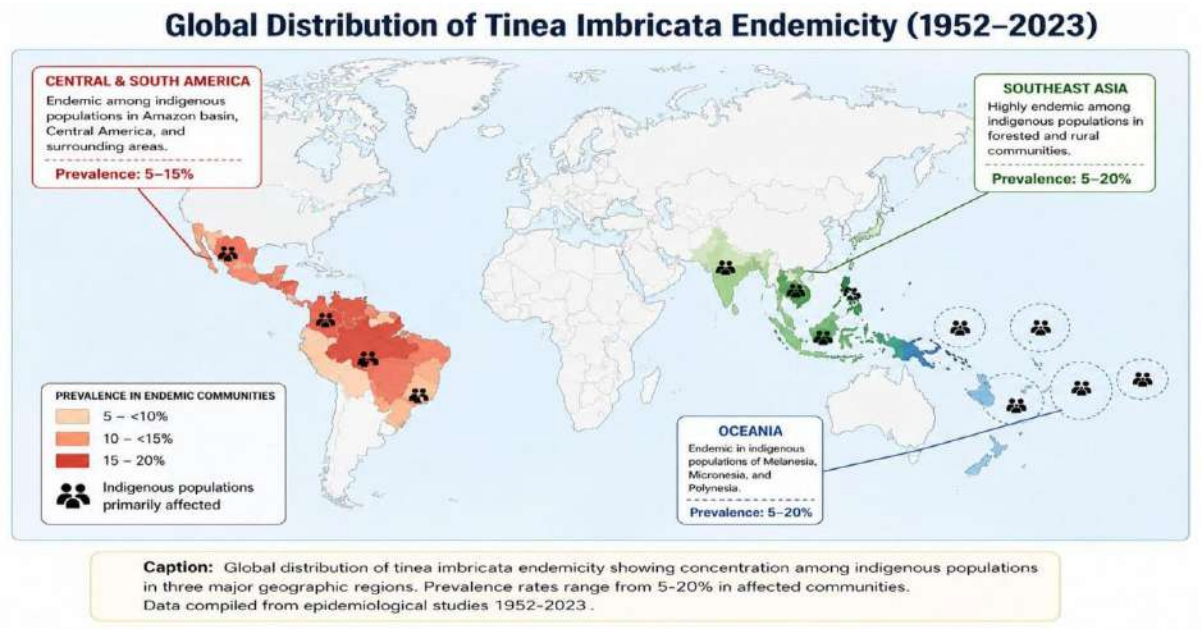

Figure 1: Global Distribution of Tinea Imbricata Endemicity

Tinea imbricata has an exceptional geographic and ethnic limitation in its epidemiology. Rates of 10-20% have been observed in some regions of Papua New Guinea and the Solomon Islands and comparable endemicity in indigenous groups in Malaysia (Orang Asli), Indonesia and remote communities in Mexico and Guatemala. The most interesting aspect of this distribution is that even with close contact over extended periods with infected people, people who belong to non-endemic populations are rarely infected, indicating that there are underlying host factors, rather than the mere exposure to the environment.

Investigators have been baffled by this paradox in more than a century. Why would a pathogen which has been sharing the human species over thousands of years still be limited to certain ethnicities even though it has plenty of chances to be cross-populated? The solution probably lies in the intersection of the host genetic architecture, skin microbial ecology, and pathogen adaptation- areas that are still largely understudied regarding this disease(Ruchti & LeibundGut-Landmann, 2023).

A clinical effect of tinea imbricata goes way beyond the physical morbidity. The affected persons develop a chronic pruritus, which becomes worse during the night causing sleep deprivation and impairment of daytime functionality. Scratching is also a common superinfection that causes the introduction of bacterial pathogens into damaged skin barriers. But the worst of all is the social stigmatization: people who have this condition may be isolated by others who are not affected, they may be discriminated against in the marriage market and they may suffer psychological stress on the same scale as that of overt disfigurements(Ruchti & LeibundGut-Landmann, 2023).

Although antifungal therapy is available, access to care in distant endemic regions is dire. The rates of recurrence are high and most of the people afflicted go through repeated courses of treatment without an ongoing cure. There is a huge economic impact on already marginalized communities and no formal cost-of-illness studies were carried out(C. Gupta et al., 2023).

In 2025, two critical advances in our knowledge of this disease have been made. First of all, molecular epidemiological tracking and identification of resistance genes have become possible due to the publication of the first reference genomes of T(Dubljanin et al., 2024). concentricum in Malaysian Orang Asli populations. Second, reports of terbinafine-resistant isolates that harbor mutations in the squalene epoxidase (SQLE) gene have cast a serious doubt on the best treatment regimens. The combination of these advances with the first in-depth skin microbiome studies in affected groups provides an unprecedented opportunity to begin to rethink tinea imbricata, first principles(Er et al., 2025).

In this review, the current knowledge is synthesized and the two less studied areas of tinea imbricata research are emphasized: the genetic susceptibility of the host and the role of the skin microbiome(Sardana, Gupta, & Mathachan, 2021). We analyze new findings in antifungal resistance and analyze current and future therapeutic approaches. We aim to discover avenues into clinically validated curative approaches that target the underlying biological determinants of this overlooked infection(Junior, Ramos, Almeida-Paes, & Frases, 2022).

We searched a total of 12 databases (PubMed, ScienceDirect, and clinical trial registries) through June 2025, using the search terms tinea imbricata, Trichophyton concentricum, host genetics, skin microbiome, antifungal resistance, and indigenous health(Galvez & Yacoubian, 2023). Articles were screened by hand on the reference lists of the retrieved articles. This was prioritized on clinical trials, genetic studies, and 2020-2025 publications and included classic older studies where they were foundational evidence.

2. Current Understanding of Tinea Imbricata Pathogenesis

2.1 The Pathogen: *Trichophyton concentricum*

T. concentricum is an anthropophilic dermatophyte that only develops in human hosts but does not have any environmental or animal reservoirs. This biological property has far

reaching impacts on the transmission dynamics and elimination plans: human-to-human transmission can theoretically be interrupted to eliminate the pathogen in isolated groups. This organism is characterised by specific biological characteristics, such as characteristic sparing of hair and nails, strong growth conditions in culture, and characteristic chlamydoconidia and no arthroconidia on a microscope(Ayuni et al., 2025).

Mycological profile: On Sabouraud agar, T. concentricum grows slowly, forming glabrous or velvety white or yellowish colonies with a typical brown pigmentation on the reverse. It is microscopically characterized by irregular hyphae containing chlamydoconidia, and lack of microconidia and arthroconidia. Although these morphological features are valuable in identification, they also indicate underlying biological variations with more common dermatophytes which might affect pathogenesis(Singhal & Grover, 2024).

Genomic discoveries: The recent sequencing of 42 T. concentricum isolates of Malaysian indigenous populations is a milestone in the study of the biology of this pathogen. The genomic analysis indicated conservation of regions with minimum genetic diversity, which implied clonal expansion in recent times or severe constraints on evolution(Liu et al., 2022). Importantly, scientists detected the mutations in SQLE gene which conferred resistance to terbinafine, which followed the trend in the emergent pathogen T. indotineae in South Asia. Molecular epidemiological tracking, resistance surveillance, and functional analysis of virulence determinants can now be accomplished by the availability of reference genomes(Grayson).

2.2 Host-Pathogen Interaction

Tinea imbricata pathogenesis is based on the interactions between fungal virulence factors and host immunity. In contrast to most dermatophyte infections, which result in inflammatory responses, T. concentricum infections are remarkably non-inflammatory indicating possible immune evasion or immune modulation abilities. This low inflammatory response is in contrast to the widespread clinical involvement and indicates a defective cell-mediated immunity against this organism(Chamorro, House, & George, 2025).

Histopathological observations: Histopathological observations of lesional skin: Compact orthokeratosis with parakeratosis, localization of hyphae in the stratum corneum, and low density of dermal lymphocytic infiltrate. It is notable that the neutrophilic infiltration is not high as in most cases of fungus. The fungal elements are very rich in the stratum corneum, but hardly reach deeper tissues, which means that the pathogenesis is limited to the upper epidermis(Spaulding, 2024).

Abnormalities of immune responses: Affected patients have reduced cell-mediated immunity to T. concentricum antigens and normal responses to other dermatophytes and remember antigens. The specificity is a strong indication of an antigen recognition or processing defect that is likely to be genetically determined(Myers, 2021). Lymphocyte transformation tests depict decreased proliferation in response to T. concentricum extracts and delayed type hypersensitivity skin tests are usually negative in the affected individuals. On the other hand, positive responses are usually observed in unaffected persons in the same communities, which implies protective immunity(Čmoková et al., 2021).

Recent findings of impaired bacterial commensals in the subjects with the disease bring interesting questions on microbiome-immune crosstalk. Both cutibacterium acnes and Staphylococcus epidermidis, which are reduced in Orang Asli with tinea imbricata are known to regulate cutaneous immune responses and generate antifungal peptides. The role of commensal depletion in the failure of antifungal immunity is unclear, with the possibility that it is also caused by it(Mayser, 2022).

Table 1. *Comparative Features of Trichophyton Species Causing Human Infection*

Feature	*T.concentricum*	*T.rubrum*	*T.indotineae*	*T.mentagrophytes*
Clinical morphology	Concentric rings, "roof tile" scaling	Annular plaques, central clearing	Inflammatory plaques, widespread	Inflammatory, vesicular
Geographic restriction	Endemic to indigenous populations	Worldwide	South Asia (emerging)	Worldwide
Hair/nailinvasion	Rare	Common	Common	Common
Inflammatory response	Minimal	Variable	Marked	Marked
Culture characteristics	Glabrous, brown reverse	Cottony, red reverse	Granular, yellow reverse	Granular, cream reverse
Chlamydoconidia	Numerous	Rare	Variable	Variable
SQLE mutations reported	Yes (2025)	Rare	Yes (epidemic)	Rare
Reference genome available	Yes (2025)	Yes	Yes	Yes

3. Host Genetic Factors: The Unexplored Frontier

3.1 Historical Evidence for Genetic Susceptibility

The tinea imbricata familial clustering has been identified long ago, but impressively scanty genetic research has been conducted. Three patterns have repeatedly been reported by observational studies that suggest genetic determinants: familial aggregation that is greater than could be due to simple exposure to shared environments; ethnic predilection among mixed populations; and discordance between spouses despite long-term intimate exposure(Chemello et al., 2023).

The best evidence is the research of polygamous native families in Mexico where Bonifaz and colleagues found patterns that were consistent with autosomal dominant inheritance. Out of 78 members of one extended family, 39 were clinically infected and multi-generational and male-to-male transmission was noticed. About half of the children of affected parents showed clinical infection which is compatible with dominant inheritance with incomplete penetrance(Notarte et al., 2023).

The opposite trend was observed in Papua New Guinea, where Ravine and co-authors reported evidence in favor of an autosomal recessive inheritance with incomplete penetrance. Their segregation studies of 228 pedigrees estimated the susceptibility gene frequency of 0.49- quite high in the case of an allele related to a disease. They were not, however, able to rule out autosomal dominant inheritance with low penetration. Such conflicting results indicate a potential genetic

heterogeneity or modifying genes and environmental factors(Shamsizadeh et al.).

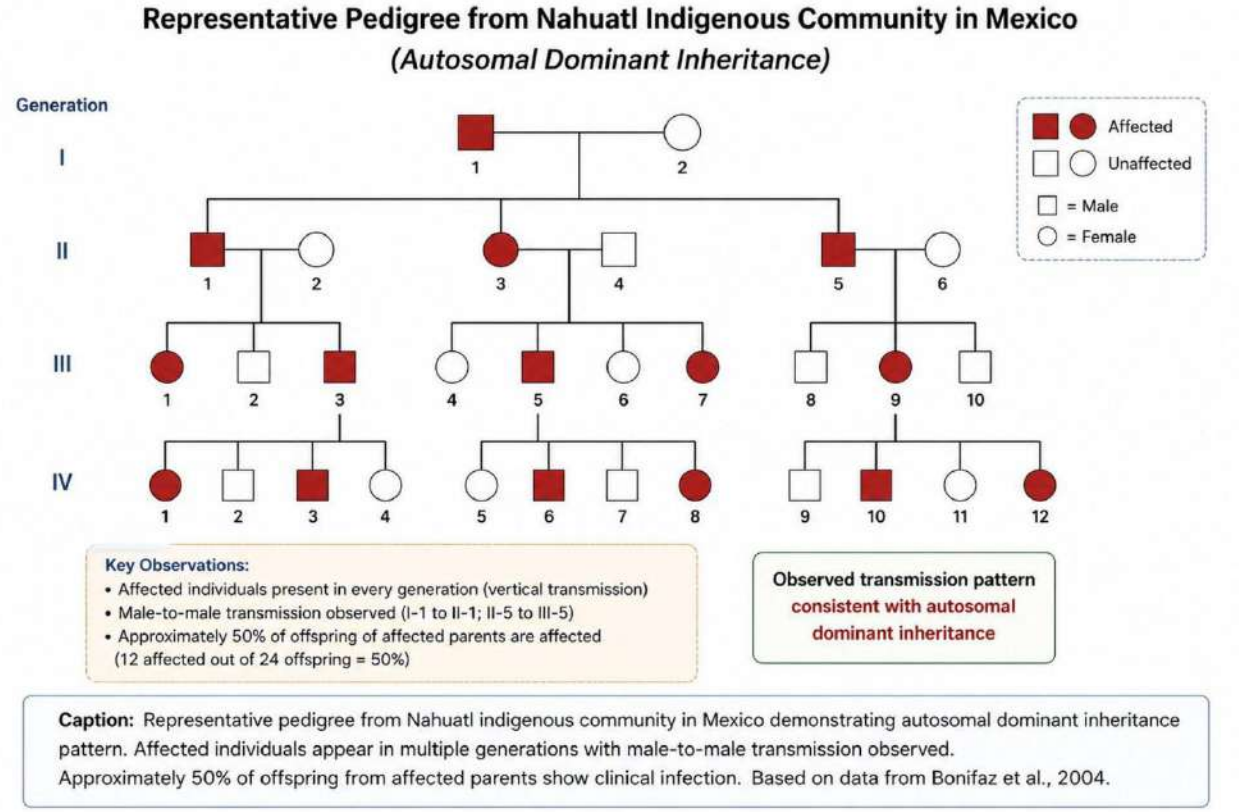

Figure 2: Pedigree Analysis of Tinea Imbricata Susceptibility in an Indigenous Mexican Family

3.2 Candidate Genes and Immune Pathways

The tinea imbricata defect in particular immunological pathway, namely the loss of cell-mediated immunity to T. concentricum antigens and the maintenance of immunity to other stimuli, indicates that the genes related to fungal recognition and T-cell activation are targeted. Logical candidates are pattern recognition receptors (PRRs) that sense fungal cell wall components, and genes of Th17 differentiation and action(Chaturvedi, Madnani, & Khan, 2023).

The CARD9-Th17 axis: CARD9 (caspase recruitment domain-containing protein 9) pathway is the focus of antifungal immunity. CARD9 is an intermediate in signaling following C-type lectin receptor (Dectin-1, Dectin-2, Mincle) which bind fungal cell wall products. Human CARD9 deficiency leads to selective vulnerability to dermatophytes and other fungi, with phenotypes strikingly similar to tinea imbricata: chronic, recurrent superficial infections unresponsive to usual treatment. Although no tinea imbricata-specific mutations of CARD9 have been reported, inherited CARD9 deficiency is associated with chronic dermatophytosis in patients that show clinical manifestations of tinea imbricata. The lack of systemic fungal infections in tinea (CARD9 deficiency usually results in invasive disease) implies that there are partial or tissue-specific defects, but not complete deficiency(Madnani, 2023).

Th17 axis which is CARD9 reliant is essential in cutaneous antifungal defense. Mice that lack interleukin-17 (IL-17) are more susceptible to dermatophyte infection and human patients with defects in the IL-17 pathway develop chronic mucocutaneous candidiasis and dermatophytosis. High-priority candidates are the IL17RA and STAT3 genes, which are required to differentiate

into Th17 and to function(Castagna & Cappelletti, 2023).

DEFB4 -2-defensin 2: The 2 -defensin 2 gene is an interesting one. Jaradat and colleagues have shown that low copy number of DEFB4 correlates with an increased susceptibility to dermatophytosis, and that the individuals with affected individuals have a higher level of systemic hBD-2 and IL-22, and this may be indicative of compensatory upregulation. β-defensins are antimicrobial peptides with direct antifungal activity and immunomodul It is still unknown whether similar processes take place in tinea imbricata.

Dectin-1 (CLEC7A): Dectin-1 is the most important receptor of 2 -glucan on myeloid cells, which recognizes the fungal cell wall and triggers antifungal immune responses. CLUC7A polymorphisms have been linked to recurrent candidiasis of the vulva and vagina and other infections. Dectin-1 has been shown to play a role in the recognition of dermatophytes in vitro and is thus a high-priority candidate gene(Leite Jr et al., 2022).

Toll-like receptors: TLR2 and TLR4 perceive the components of dermatophytes and control the inflammatory reaction. The susceptibility to tinea pedis and chronic dermatophytosis has been linked to polymorphisms in these genes. They have not been studied with regard to their possible role in tinea imbricata(Gnat, Nowakiewicz, Łagowski, & Zięba, 2019; Hoffman et al., 2022; Ruiz-Cano & Arnao, 2024).

Table 2. ***Candidate Genes Implicated in Dermatophyte Susceptibility***

Gene	Protein	Function	Evidence in Dermatophytosis	Potential Relevance to Tinea Imbricata
CLEC7A	Dectin-1	β-glucan receptor, fungal recognition	Polymorphisms associated with recurrent vulvovaginal candidiasis; role in dermatophyte recognition demonstrated in vitro	High - critical for antifungal immunity
TLR2	Toll-like receptor 2	Fungal ligand recognition	Associated with tinea pedis susceptibility; regulates inflammatory response	Moderate - may influence clinical phenotype
TLR4	Toll-like receptor 4	Fungal ligand recognition	Polymorphisms linked to chronic dermatophytosis	Moderate
DEFB4	β-defensin 2	Antimicrobial peptide	Low copy number associated with dermatophytosis susceptibility	High - fungal killing and immune modulation

CARD9	Caspase recruitment domain 9	Dectin-1 signaling pathway	Mutations cause profound susceptibility to dermatophytes and other fungi	High - but typically causes severe disseminated disease
IL17RA	IL-17 receptor A	Th17 signaling	Essential for cutaneous antifungal defense	High - Th17 responses critical for dermatophyte control
STAT3	Signal transducer and activator of transcription 3	Th17 differentiation	Mutations cause Job's syndrome with dermatophyte susceptibility	Moderate - typically associated with broader defects

3.3 Research Gaps in Host Genetics

Suggestive evidence notwithstanding, a study of tinea imbricata susceptibility has not been performed yet on a genome-wide association scale (GWAS). Lack of big, well-characterized cohorts and the distance of affected populations have been an obstacle. Some of the unresolved questions are:

Is it monogenic or polygenic susceptibility? These conflicting inheritance patterns reported can be due to real genetic heterogeneity or the effect of multiple genes with variable penetrance. Answering this question will need large-scale genetic analyses that are adequately powered to identify both major-effect and modest-effect variants(Gnat et al., 2019).

How important is the HLA type? Linkages between HLA class II alleles and infection by dermatophytes have been reported in other species but not in tinea imbricata. This is a big gap considering the central role of HLA in antigen presentation and subsequent T-cell activation(Hay, 2020).

Are there protective genotypes? Asymptomatic carriers within high-endemic populations might carry protective genetic variants; their discovery can shed light on the resistance mechanisms and provide therapeutic options.

What is the interaction of genetic factors with the microbiome? Host genotype affects the composition of skin microbiome which can also impact the vulnerability to pathogenic fungi. These interactions will be hard to understand without combined genetic and metagenomic analyses(Tuknayat, Bhalla, Kaur, & Garg, 2020).

3.4 Proposed Genetic Research Agenda

To deal with these gaps, it is necessary:

1. Well-phenotyped indigenous population genome-wide association studies with a minimum of 500 cases and 1000 population-matched controls(Camargo-Sánchez et al., 2019).
2. Entire-exome or entire-genome sequencing of multiplex households (several impacted people throughout generations)(Mayser & Gräser, 2019).
3. Prioritised pathway candidate gene association studies (CARD9, IL-17, DEFB4, CLEC7A)(Tuknayat, Bhalla, Amrit Kaur, & Garg, 2020).
4. Practical research on the recognized variants of the model cells (dendritic cell-fungal co-culture, T-cell proliferation assays)(Gunaydin, Arikan-Akdagli, & Akova, 2020).
5. Analysis of gene-environment interactions including variables of microbiome composition and exposure(J. Ahmad, 2020).

4. Skin Microbiota: The Missing Link

4.1 The Skin Microbiome in Health and Disease

The human skin accommodates various communities of bacteria, fungi, viruses, and

archaea that work together to achieve a barrier effect and immunological training. The commensal organisms secrete antimicrobial peptides, outcompete the pathogens with nutrients and adhesion surfaces, and control local inflammatory. This microbial ecosystem is dynamic and is responsive to the host genetics, environmental exposures, hygiene practices and disease states(Sarkar & Sinha, 2019).

Major bacterial commensals, such as Cutibacterium acnes, Staphylococcus epidermidis and Corynebacterium species, predominate on healthy skin sites. These organisms have been demonstrated to prevent dermatophytes growth both in vitro and in vivo in various ways. S. epidermidis secretes modulins able to kill fungi which are soluble in phenol and secretes serine proteases that break up fungal adhesins. C. acnes effectively exploits lipids on the skin, which could cause a lack of substrate available to lipid-dependent dermatophytes. The two organisms regulate the cutaneous immune responses, which encourages Th17 responses that are essential in suppressing fungi(Lopes, Tavaria, & Pintado, 2020).

4.2 Microbiome Alterations in Tinea Imbricata

In 2025, the initial study to provide a comprehensive analysis of skin microbiomes in tinea imbricata was published comparing 82 Orang Asli with urban Malaysian and US populations. The results were dramatic: the relative abundances of protective commensals of indigenous people with a disease were significantly lower than those of urban populations, especially C. acnes and S. epidermidis(Lopes et al., 2020).

Notably, the research also reassembled 437 new prokaryotic metagenome-assembled genomes (MAGs) of native skin samples, significantly increasing the diversity of the known human skin microbiome. Numerous of these new organisms were exclusive to local groups and never seen in urban cohorts, and underline the importance of understudied groups providing unprecedented biological discoveries. It is not known at all what functional properties these new organisms will have: what will their metabolic activity, what will be their antimicrobial production and what will be their interactions with the immune system(Suhonen, Dawber, & Ellis, 2020).

The urbanization gradient: Partially urbanized indigenous people exhibited intermediate microbiome structure, indicating that microbial community structure is mediated by lifestyle (hygiene practices, clothing, housing materials, diet). This finding poses basic questions regarding the effects of modernization on skin microbial communities and how this would affect susceptibility to infectious diseases(Caldwell, 2020).

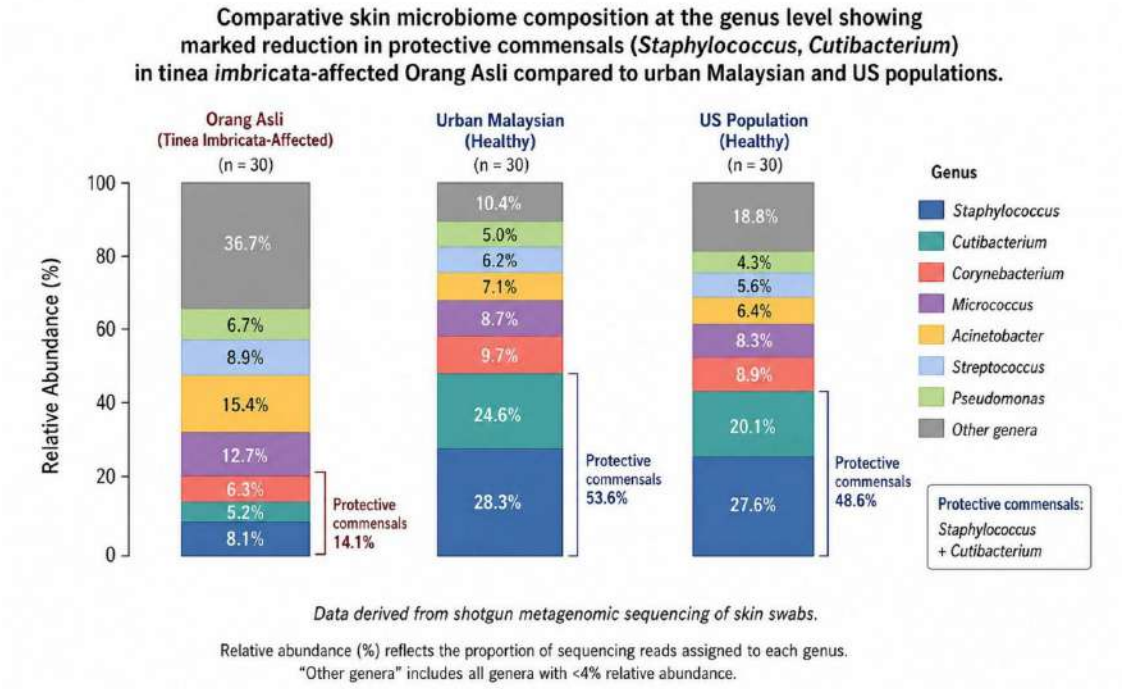

Figure 3. Skin Microbiome Composition in Tinea Imbricata-Affected versus Healthy Individuals

4.3 Mechanistic Hypotheses for Microbiome-Mediated Protection

The decreased levels of protective commensals in people with the condition can help predispose it in a number of ways:

Direct antifungal action: Commensal bacteria generate various antifungal substances. S. epidermidis causes fungal membrane disruption with the production of phenol-soluble modulins. Antifungal compounds are generated by other commensals as organic acids, bacteriocins, and volatile compounds. The loss of these organisms can form a microenvironment that will be conducive to fungal proliferation.

Resource competition: The stratum corneum has a restricted supply of nutrients, i.e., lipids, amino acids, and trace metals. C. acnes has an efficient use of lipids in the skin, which may restrict its substrate availability to T. concentricum. Commensal depletion can result in higher nutrient levels in the pathogen(Loke et al., 2026).

Immune modulation: Commensal bacteria train the cutaneous immune system to enhance Th17 cells that are important in antifungal immunity. S. epidermidis particularly provokes IL-17-producing T cells which prevent the attack of fungal pathogens. A decrease in the abundance of commensals can contribute to the lack of immune surveillance and response(Akarawita & Kahawita, 2026).

Barrier enhancement: Commensal organisms improve epithelial barrier competence by regulating tight junctions and by synthesizing mucin. Weakened barrier can lead to fungal invasion and survival(A. K. Gupta et al., 2026).

4.4 The Causality Question: Cause or Consequence?

The most important unsolved problem is whether changes in microbiome observed are cause or effect of infection. Three possibilities exist:

Preexisting dysbiosis: Patients with naturally low concentrations of protective commensals are perhaps more prone to colonization and infection by T. concentricum. This may be due to host genetic factors (e.g. genes influencing the production of antimicrobial peptides), environmental exposures (e.g. diet, hygiene practices) or early-life microbial colonization

patterns(Chanyachailert, Leeyaphan, & Bunyaratavej, 2023).

Dysbiosis caused by infection: Fungal overgrowth could actively displace bacterial commensals by competition, antifungal secretion or immune regulation. T. concentricum can release compounds which prevent bacterial growth or cause host responses which collaterally damage commensals(Vinh, 2025).

Bidirectional relationship: A vicious cycle where dysbiosis allows infection, which further destabilizes microbiomes, which, in turn, causes disease. The model forecasts that a reduction in relapse would come with the restoration of commensals following the antifungal treatment(Chiriac, Nenoff, & Wollina, 2025).

To differentiate these possibilities, longitudinal studies of the at-risk individuals prior to infection, during active disease, and after successful treatment are needed. These studies have not been carried out.

4.5 The Hygiene Hypothesis Connection

The clear discrepancy in microbiome composition between native and urban inhabitants poses interesting questions about the hygiene hypothesis to tinea imbricata. Conservative lifestyles, such as low levels of soap use, communal water sources, contact with soil and close-knit living conditions could encourage a microbiome that is both healthy (low atopic disease) and hospitable to some pathogens. This trade-off is important to understand how to design interventions that do not alter the beneficial microbial ecology(Middleton et al., 2023).

5. Current Treatment Landscape and Emerging Resistance

5.1 Established Therapeutic Approaches

Systemic antifungals have historically been used in the treatment of tinea imbricata with topical therapy being viewed as an adjunct owing to the large body surface area usually involved. The latest randomized controlled trial (RCT) in tinea imbricata is the one by Wingfield and others in 2003, which compared griseofulvin, terbinafine, itraconazole, and fluconazole in 59 patients in an indigenous population(Mustaffa et al., 2026).

Terbinafine: In the RCT, terbinafine 250mg/day over 4 weeks had a mycological cure rate of over 90 with 8+ weeks of sustained remission after treatment. The mechanism of action of terbinafine is the inhibition of the production of ergosterol, which is made possible by inhibiting squalene epoxidase, which makes terbinafine have fungicidal effects against dermatophytes. It is an appealing first-line agent due to its positive safety profile, once-daily dosing, and excellent skin penetration. Nevertheless, recurrence in six months affects 40-60 percent of those patients who are treated successfully and the recent report of resistance endangers its use(Ismail, Shariffuddin, Sayed, Alias, & Mamat, 2025).

Griseofulvin: The classic griseofulvin 500 mg twice a day 4-8 weeks, has the highest cure rate (70-85) but increased recurrence (50-70). Griseofulvin discourages the polymerization of microtubules in the fungi, preventing mitosis. Its shortcomings are lengthy course, fluctuating absorption (increased during fatty meals), interactions with other drugs (warfarin, oral contraceptives), and possible teratogenicity (not to be used during pregnancy). Regardless of these cons, griseofulvin is still commonly used in resource limited environments because of its low cost and extended duration(Sompotan, 2025).

Itraconazole: Itraconazole 200 mg/day/4weeks is curative with 70-90% but with lower remission time than terbinafine. The mechanism of itraconazole is by inhibition of fungal cytochrome P450-dependent enzymes that inhibit ergosterol synthesis. Its use is restricted by variable absorption (must be used in acidic gastric pH), drug interactions (a variety of CYP3A4 substrates), and hepatotoxicity(Adna & Aruan, 2022).

Fluconazole: The RCT reported that fluconazole 200 mg once a week during 4 weeks did not result in a significant remission and this agent is not used in tinea imbricata. The current dosing schedule is weekly, which is convenient, but may give inadequate exposure to the drug to be effective in treatment(Hill, Caplan, et al., 2024).

Topical therapy: Topical antifungals have a cure rate of 30-50% in tinea imbricata, which is largely because the body surface area covered is often extensive and deep penetration in thickened scales is inadequate. A recent retrospective study, however, demonstrated that topical monotherapy with terbinafine 1% gel was as effective as combining it with oral griseofulvin in the case of limited disease, thus indicating a possible role of topical monotherapy in mild cases(Barac et al., 2024).

Table 3. ***Clinical Evidence for Antifungal Agents in Tinea Imbricata***

Agent	Dose	Duration	Cure Rate	Recurrence Rate	Evidence Level	Notes
Terbinafine	250 mg daily	4 weeks	75-95%	40-60% at 6 months	Randomized trials	Current drug of choice; resistance now documented
Griseofulvin	500 mg twice daily	4-8 weeks	70-85%	50-70%	Multiple studies	Historical standard; safe in pregnancy
Itraconazole	200 mg daily	4 weeks	70-90%	45-65%	Randomized trials	Alternative for terbinafine failure
Fluconazole	150-300 mg weekly	4-6 weeks	60-75%	55-70%	Limited data	Less effective than daily dosing
Ketoconazole	200 mg daily	4 weeks	65-80%	50-65%	Older studies	Hepatotoxicity concerns limit use
Topical antifungals	Various	4-8 weeks	30-50% alone	High	Case series	Adjunctive only; impractical for extensive disease
Senna alata decoction	Daily application	4 weeks	Limited data	Unknown	Pilot trial	Traditional remedy; requires validation

5.2 The Emergence of Terbinafine Resistance

The 2025 identification of terbinafine-resistant T. concentricum strains fundamentally changes the picture of treatment. Out of 42 Malaysian Orang Asli community clinical isolates, 7 (16.7) exhibited high minimum inhibitory concentrations to terbinafine and microbiological resistance was also supported by genomic identification of SQLE gene mutations(Wijayawardene et al., 2024).

Mechanisms of resistance: The resistant strains contained point mutations in the SQLE gene, which encodes the target enzyme of terbinafine, squalene epoxidase. Such mutations modify the binding site of the enzyme with a decrease in terbinafine affinity and maintenance of catalytic activity. The identified mutations are both those reported in T. rubrum and T. indotineae and possibly new ones(Bhuiyan et al., 2024).

Epidemiology: The resistant strains had a geographical concentration but were not limited to one village indicating that they were either spread through clonal means or emerged under selective pressure. Topical antifungals are available over the counter and may contribute to resistance as observed in the epidemic of T. indotineae in South Asia due to the use of combination products with corticosteroids. The occurrence of resistance beyond Malaysia is not clear(Hill, Gold, & Lipner, 2024).

Clinical implications: Terbinafine at standard dose is unlikely to work with the resistant strains. In the case of patients who do not respond to terbinafine therapy, the use of other agents (itraconazole, griseofulvin) should be considered, but there is no evidence of their effectiveness against resistant strains. Synergistic effects of combination therapy (e.g., terbinafine plus itraconazole) can potentially overcome resistance, although no clinical trial evidence is available(Nosratabadi et al., 2024).

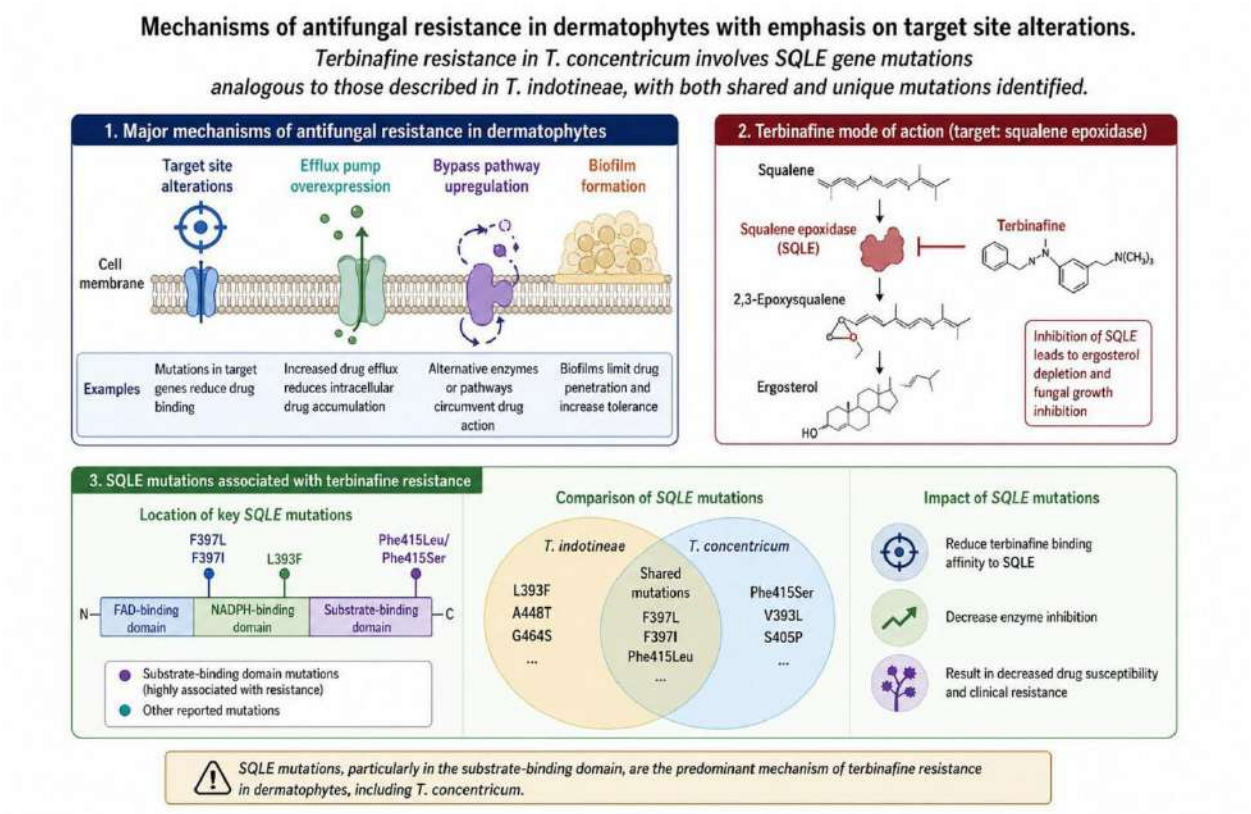

Figure 4. Mechanisms of Antifungal Resistance in Dermatophytes

5.3 Implications for Treatment Guidelines

The development of terbinafine resistance requires change of treatment algorithms. Key considerations include:

Baseline resistance testing: Susceptibility testing should be used to direct initial therapy where available. SQLE mutations can be molecularly detected and these resistant strains can be identified quickly but this is not common in

most endemic areas. Research should focus on development of point-of-care resistance tests.

Other first-line agents: Itraconazole or griseofulvin can be used as the first choice in the areas where resistance has been reported until the susceptibility is reported. Nevertheless, their efficacy is less and recurrence rates are elevated even in susceptible strains(L. Zhang et al., 2025).

Combination therapy: It is logical to consider combining systemic and topical antifungals with keratolytic agents, which should be formally tested in randomized studies. Adjunctive agents can be topical agents with alternative mechanisms of action (e.g., ciclopirox olamine)(de Oliveira Alves et al., 2025).

Duration of treatment: Resistant strains can take extended therapy, or increased doses, but clinical evidence is not available. Cases that are challenging may be guided by therapeutic drug monitoring when administering drugs.

Surveillance networks: Resistance surveillance programs in all endemic areas must be established immediately. Methods of standardized susceptibility testing of T. concentricum need to be developed and validated(Mirhendi et al., 2025).

5.4 Pipeline Therapies and Novel Approaches

A number of new approaches have potential in the treatment-refractory tinea imbricata:

New antifungals: Newer agents under development, such as Olorofim (an anti-dihydroorotate dehydrogenase agent) and rezafungin (a long-acting echinocandin) have not been tested in dermatophytes, but may be considered in cases of multidrug-resistance. The Fosmanogepix (against Gwt1) and Ibrexafungerp (glucan synthase inhibitor) are also widely acting antifungals(Shao et al., 2025).

Microbiome-friendly therapies: With the discovery of protective bacterial commensals, there is potential to improve treatment with microbiome restoration. S. epidermidis or C. acnes strains as live biotherapeutic products are theoretically attractive but would need stringent safety and efficacy trials. Possible solutions involve the use of topical probiotic preparations following antifungal treatment, prebiotic preparations where commensals are selectively stimulated to grow, or transplantation of microbiomes of healthy donors.

Traditional medicines: In the Philippines, Senna alata (Akapulko) leaf decoction has been a traditional medicine, and a pilot clinical trial showed it to be feasible to evaluate it formally. Although there is not much efficacy data, serious research on traditional remedies may find treatment solutions that are affordable and available to remote communities. There are other traditional preparations employed in the endemic areas that should be systematically investigated(De Hoog et al., 2017).

Immunomodulatory techniques: In patients with proven genetic defects of immune, antifungal immunity-enhancing strategies are theoretical. TLR7 agonist (imiquimod topical) boosts Th1 responses and has been used in other dermatophytases. Antimicrobial peptide production is increased by topical vitamin D analogs. Systemic IFN- G has been applied in chronic granulomatous disease and fungal infections that are refractory. None have been tested in tinea imbricata(Martinez-Rossi, Peres, Bitencourt, Martins, & Rossi, 2021).

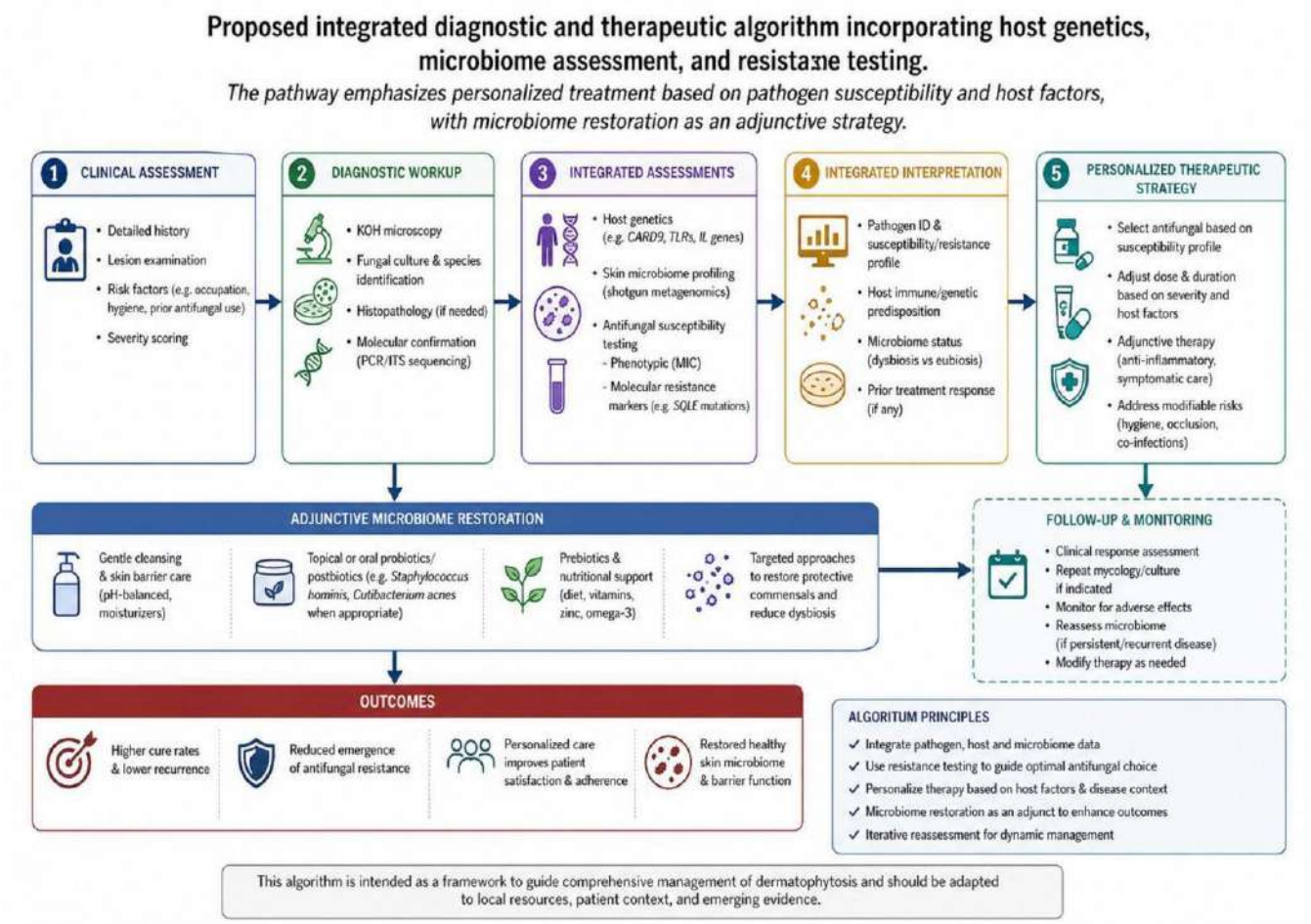

Figure 5. Integrated Therapeutic Strategy for Tinea Imbricata

6. Knowledge Gaps and Research Priorities

6.1 Major Unanswered Questions

In spite of recent developments, there are still unanswered basic questions in tinea imbricata. The most severe gaps are related to epidemiology, pathogenesis, treatment, and prevention.

Epidemiology: What is the actual prevalence of tinea imbricata all over the world? Most endemic areas do not have any systematic surveys. Is there any importance of asymptomatic carriers in transmission? Incidence rate (infection new cases per person-year) in endemic communities? What is the mode of transmission at the household and community level?

Pathogenesis: How can the molecular basis of host genetic vulnerability be elucidated? Is the skin microbiome causal or just a manifestation of infection? What are the immune processes that eliminate T. concentricum in others? Which virulence factors help T. concentricum to avoid host defenses?

Treatment: What is the ideal length of treatment of terbinafine? Is combination therapy able to overcome terbinafine resistance? Are probiotics/microbiome restoration therapeutic? Is there efficacy of newer topical agents (luliconazole, efinaconazole, tavaborole)?

Resistance: How common is terbinafine resistance in endemic areas? Do cross-resistance patterns have predictability? Is resistance able to develop during treatment (as opposed to primary resistance)? What are the clinical predictors of resistance?

Prevention: Can decontamination at the household level be effective? Is health education able to decrease transmission? Would mass administration of drugs get rid of tinea imbricata

in isolated communities? Is it possible to create a vaccine?(Mapook et al., 2022)

Table 4. *Critical Knowledge Gaps in Tinea Imbricata Research*

Domain	Current Knowledge	Critical Gaps	Research Priority
Host genetics	Familial clustering documented; candidate genes proposed	No GWAS; unknown heritability; protective alleles unidentified; gene-environment interactions unexplored	High - GWAS in endemic populations essential
Skin microbiome	Reduced commensals in affected individuals; novel MAGs identified	Causality unclear; longitudinal dynamics unknown; functional mechanisms undefined; intervention studies absent	High - Longitudinal and interventional studies needed
Pathogen genomics	Reference genomes available; resistance mutations identified	Global strain diversity unknown; transmission dynamics unclear; virulence factors undefined; evolutionary history unexplored	Medium - Geographic expansion of genomic surveillance
Antifungal resistance	Terbinafine resistance documented; SQLE mutations identified	Resistance prevalence unknown; geographic distribution unclear; clinical outcomes with resistance undocumented; alternative agents untested	High - Resistance surveillance network needed
Treatment outcomes	Recurrence rates high; terbinafine most effective	No RCTs in most endemic regions; optimal duration undefined; combination therapy untested; microbiome-based interventions unexplored	High - Pragmatic trials in endemic settings
Immunopathogenesis	Impaired cell-mediated immunity documented	Specific immune defect unknown; role of Th17 undefined; memory responses uncharacterized; vaccine potential unexplored	Medium - Mechanistic immunology studies

Social determinants	Associated with poverty and isolation	Relative contribution of environmental vs. genetic factors unknown; intervention effectiveness for social determinants untested	Low - Implementation research needed

6.2 The Central Gap: Causal Relationships

The unanswered question most in need of attention is whether changes in the microbiome are cause or effect of infection. To draw the line between these possibilities, longitudinal studies of these individuals at risk before infection, during the active disease, and after successful treatment are necessary. These studies have not been carried out(Rodrigues Hoffmann, Ramos, Walker, & Stranahan, 2023).

Another gap that relates to it is the lack of functional studies on mechanisms of commensal-mediated protection. Does S. epidermidis and C. acnes have a direct effect of inhibiting the growth of T. concentricum? Do they regulate immune responses such that they improve fungal clearance? Do certain strains offer greater protection compared to others?(Naik, Ahmed, Laha, & Das, 2021).

6.3 The Promise of Multi-Omics Integration

The gaps that need to be addressed require an integrated strategy that involves genomics, metagenomics, transcriptomics, and immunology.

The optimal study design would:

- Recruit whole communities in endemic areas, including infected and uninfected persons.
- Take longitudinal samples (skin swabs, scrapings, blood) at various time points.
- Conduct host genotyping (GWAS or whole-genome sequencing).
- Perform shotgun metagenomic sequencing of skin microbiomes.
- Isolate and sequence T. concentricum strains to do genomic analysis(Martins-Santana, Rezende, Rossi, Martinez-Rossi, & Almeida, 2023).
- Determine immune reactions to fungal antigens (lymphocyte proliferation, cytokine production)
- Environmental exposures of documents, hygiene, and social factors.
- This detailed data would facilitate causal inference (Mendelian randomization and longitudinal modeling), and would help determine intervention targets(Prajapati, Jain, & Bajpai, 2025).

6.4 Prioritized Research Agenda

Immediate priorities (1-2 years):

- Multi-centre prevalence surveys with standard diagnostic criteria.
- Future cohort studies to determine the risk factors in both acquisition and persistence(Li et al., 2025).
- Genomic surveillance of antifungal resistance in all endemic areas.
- Kinetic Pharmacokinetic investigations of oral antifungals in malnourished indigenous people.

Medium-term priorities (3-5 years):

- Susceptibility association study (genome-wide) (also needs multi-site cooperation)(Brown et al., 2024).
- Randomized controlled trial of extended-duration terbinafine (8-12 weeks) in cases of resistance.
- Combination therapy (terbinafine + itraconazole) clinical trial in confirmed resistance.
- Topical commensal restoration (Skin microbiome intervention trial).
- Long-term priorities (5-10 years):
- Vaccine development (against T. concentricum antigens)

- Studies of gene-environment interaction that include exposure data and microbiome data(Shah, Mirza, Sattar, Khan, & Khan, 2025).
- Elimination program implementation science with indigenous communities.
- Skin microbiome intervention trial (topical commensal restoration)

Long-term priorities (5-10 years):

- Vaccine development (targeting *T. concentricum* antigens)
- Gene-environment interaction studies incorporating microbiome and exposure data
- Implementation science for elimination programs in indigenous communities(I. Ahmad et al., 2023).

7. Toward Clinically Proven Cure: A Proposed Framework

7.1 Defining "Cure" in Tinea Imbricata

Tinea imbricata has been inconsistently defined as clinically cured, and thus, cross-study comparisons are difficult. We suggest standardized criteria:

Complete cure: Full clinical healing of all lesions with negative mycological testing (KOH and culture) long-term (12 months off treatment) without evidence of microbiome replacement (commensal abundances returned to normal controls of a healthy community)(A. K. Gupta, Polla Ravi, Wang, Bakotic, & Shemer, 2024).

Clinical remission: Full clinical remission and negative mycology maintained 6 months.

Response to treatment: 75 percent decrement in the size of involved body area with negative mycology at the end of treatment.

Recurrence: Lesions with positive mycology reappear after cure has been documented, which is differentiated by relapse (with the same strain by genotyping) and reinfection (with a different strain)(Baron et al., 2024).

7.2 Evidence-Based Treatment Algorithm

Using the available evidence and the new data on resistance, we suggest the following algorithm:

First-line (susceptible strains, limited disease): Terbinafine 1% gel single dose per day 4-8 weeks, continuing until 2 weeks after clinical clearance. Keratologic agent (salicylic acid 3-6%) could be used topically to increase penetration and scale removal.

First-line (susceptible strains, extensive disease): 250 mg of terbinafine orally daily during 4 weeks. Combine topical terbinafine with synergy (but combination has not been shown to be better than monotherapy)(Neves-da-Rocha, Santos-Saboya, Lopes, Rossi, & Martinez-Rossi, 2023).

First-line (resistance documented or suspected): Itraconazole 200 mg/day 4 weeks OR griseofulvin 500 mg/day twice a day 6-8 weeks. Refractory cases should be considered as combination therapy (e.g., itraconazole + topical ciclopirox).

Failure to respond (no response at 4 weeks): Re-establish diagnosis (repeat KOH/culture), perform susceptibility testing where possible, use alternative agent, extend therapy to 8-12 weeks(Markantonatou, Samaras, & Vyzantiadis, 2023).

Adjunctive treatment to everyone: Microbiome-protective interventions such as soft cleansing (without using antimicrobial soaps), moisturization, and attention to the use of probiotic-containing preparations after confirmation. Nutritional assistance to the malnourished.

Post-treatment surveillance: Monthly clinical check-up, 6 months followed by quarterly, 12 months, with immediate retreatment of recurrence based on susceptibility tests(Arya et al., 2025).

7.3 The Microbiome Restoration Hypothesis

In case lower commensals are a contributing factor to vulnerability, then restoration of microbiomes may improve the cure rate and avoid reoccurrence. Testable interventions include:

Probiotic use: Topical preparations of live S. epidermidis or C. acnes strains used post-antifungal therapy. The main issues are the selection of strain (not all strains are protective), stability of formulations (viable bacteria in topical vehicle), dose schedule, and the safety in immunocompromised patients(Zhang, Xie, Liu, Li, & Liang, 2025).

Microbiome transplantation: Microbiota on the skin of healthy, resistant community members transferred to affected individuals (similar to fecal transplantation). This method would relocate whole communities of commensals, possibly unculturable organisms. Technical issues are standardization, safety and acceptability.
Prebiotic support: Prebiotic preparations that selectively stimulate growth of protective commensals. Examples are lipids which promote C. acnes growth or certain carbohydrates which promote useful staphylococci(Mousavi et al., 2023).
Lifestyle interventions: Hygiene practice to aid commensal re-establishment. This could involve the use of fewer antimicrobial soaps, traditional practices which encourage microbial diversity or changes in diet(Galgóczy, 2025).

7.4 Genetic Counseling and Family-Based Prevention

Genetic counseling may guide preventive measures in families that are known to have inherited susceptibility:
Early screening: Infrequent skin tests on children at risk starting in infancy. Parental education on infection early signs to treat early.
Prophylactic measures(Kroustali et al., 2025): Topical antifungal or probiotic prophylaxis in the high-exposure period in genetically vulnerable people. There have been no prophylactic studies.
Family-based treatment: Treatment of the entire family at the same time to avoid reinfection cycles. Environmental decontamination (bedding, clothing, common bathing spaces, etc.) at the household level can also help to reduce transmission(Zalewski, Goldust, & Szepietowski, 2022).

7.5 Community-Level Elimination Strategies

In isolated populations where disease levels are high, eradication can be possible with concerted public health efforts:
Mass drug administration: Would need safe, effective oral agents that can be used massively. Terbinafine is suitable with regard to safety profile but resistance is a problem to this method. Griseofulvin is less powerful and has more contraindications.
Intervention on household level: Multisensitized therapy of all the affected individuals in the household and environmental decontamination. Educational measures to minimize sharing of clothes and towels(Mahajan et al., 2025).
Surveillance and response: Active case finding, prompt treatment, and contact tracing to break chains of transmission.
Vaccination: Long-term objective that involves discovery of protective antigens and establishing a suitable vaccine platform(Ortiz et al., 2024).

8. Conclusions

Tinea imbricata is an intermediate in science. The overlap of the recently emerging pathogen genomics, new forms of antifungal resistance, and unexamined understanding of the diversity of the skin microbiome in indigenous populations pose a pressing challenge and a unique opportunity. The report of terbinafine-resistant T. concentricum requires urgent review of the treatment guidelines and development of resistance surveillance systems in the foci.
But no, the part of resistance is not all. Such far-reaching questions as to which populations this disease is specific, why it recurs in families, why it is so widespread, are directed at the underlying biological processes at the interplay between host genetics, microbiome ecology, and pathogen adaptation. The stunning disparities in the skin microbiome composition of indigenous and urban groups and recovery of hundreds of novel bacterial genomes of infected individuals are reminders of the fact that much remains to be learned about human-microbe co-evolution.
The discipline faces three knowledge gaps that are of utmost importance and need to be closed as a matter of priority:
To begin with, tinea imbricata susceptibility has never been studied in a genome-wide association study. The autosomal recessive model was proposed 40 years ago and, since then, there is no mapped susceptibility locus. No published studies of candidate genes have been done. Molecular pathogenesis of familial clustering is completely unknown.

Second, there is only one study of the microbiome of the skin. No longitudinal studies investigate the changes in microbiome before, during and after infection. Microbiome restoration has not been tested in any intervention studies. It is not clear how dysbiosis leads to infection.

Third, there is no systematic surveillance on antifungal resistance. Resistance is a sentinel discovery in the 2025 resistance report, but there is no information on its generalizability. There are no standardized methods of susceptibility testing of T. concentricum. Endemic regions are not connected by any surveillance networks.

To attain a proven clinical cure of tinea imbricata, it will be necessary to go beyond a one-size-fits-all antifungal treatment and to the use of personalized treatment with host genetic risk factor, microbiome status, and pathogen resistance profiles. This vision demands:

Basic research: GWAS, longitudinal microbiome, and mechanistic immunology of endemic populations. Such studies should be properly financed and should have a good statistical power.

Clinical trial infrastructure: Pragmatic trials as part of a community health system, testing both traditional and new therapies. The design of the trials should consider the actualities of remote environments and be scientifically rigorous.

Capacity building: Educating indigenous health workers to do research and provide evidence-based care. It is not about extractive research but needs to develop local expertise and infrastructure.

Fair collaborations: Indigenous sovereign research relationships that consider community needs and priorities and provide sharing of benefits. Affected communities of tinea imbricata need to be given a say in the research agenda and access to research outputs.

The course of action is scientifically difficult and morally obligatory. To the indigenous population that has been the most affected by the unique and stigmatizing disease over the centuries, the hope of a carefully-tested and scientifically-validated cure must come true. There is now a set of tools available, such as genomics, metagenomics, advanced trial designs, and community-engaged research, which can finally break the cycle of tinea imbricata. The only thing needed is the political will, funding of the research and cooperative spirit to utilize these tools successfully.

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