**Sriwijaya Journal of Otorhinolaryngology** e-ISSN 2987-131X
https://phlox.or.id/index.php/sjorl Vol. 3 No. 2 (2025)

*Systematic Review and Meta-Analysis*

# Comparative Efficacy of Topical Antifungal and Antiseptic Agents for Otomycosis in Tropical and Subtropical Climates: A Systematic Review and Meta-Analysis

Rachmat Hidayat[1,*], Oliva Azalia Putri[2], Aisyah Andina Rasyid[3]

[1]*Department of Medical Biology, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia*
[2]*Department of Thoracic Surgery, CMHC Research Center, Palembang, Indonesia*
[3]*Department of Otorhinolaryngology, CMHC Research Center, Palembang, Indonesia*

**ARTICLE INFO**

**Article history:**
**Received:** *August 20, 2025*
**Accepted:** *September 21, 2025*
**Published:** *October 30, 2025*

**Keywords:**
Antifungal agents
Clotrimazole
Otomycosis
Povidone-iodine
Tropical climate

***Corresponding author:**
Rachmat Hidayat
E-mail:
dr.rachmat.hidayat@gmail.com
ORCID: *0000-0001-5770-1201*

**Registration:** PROSPERO CRD420261456091
**DOI:** 10.59345/sjorl.v3i2.305

**ABSTRACT**

**Background:** Otomycosis is a superficial fungal infection of the external auditory canal that is disproportionately prevalent in tropical and subtropical regions, yet the comparative efficacy of topical agents in this climatic and mycological context has not been quantitatively synthesised.

**Objective:** To compare complete-cure rates of topical antifungal and antiseptic agents for otomycosis using comparative studies from tropical and subtropical countries.

**Methods:** Following a registered protocol (PROSPERO CRD420261456091) and PRISMA 2020, we identified comparative studies reporting complete cure or mycological eradication. Ten studies (1,970 ears; eight countries) were included. The pre-specified primary comparison, povidone-iodine versus clotrimazole, was pooled as a risk ratio (RR) using a random-effects model with the Hartung–Knapp–Sidik–Jonkman correction, a 95% prediction interval and a leave-one-out analysis. Risk of bias used RoB 2 and ROBINS-I; certainty used GRADE.

**Results:** The random-effects pooled cure rate across 21 arms was 74.9% (95% CI 66.9–82.2; $I^2$ = 93%). For povidone-iodine versus clotrimazole (k = 4), the pooled RR was 0.86 (HKSJ 95% CI 0.53–1.39; prediction interval 0.29–2.58), indicating no significant difference while excluding neither agent's superiority. Between-study heterogeneity ($I^2$ = 79%) arose entirely from one non-randomised study; omitting it gave RR 0.95 (0.85–1.06) with $I^2$ = 0%. Certainty was low to very low.

**Conclusion:** Topical azoles and low-cost antiseptics such as povidone-iodine achieve broadly similar, moderate cure rates for otomycosis in tropical settings, but the evidence is too imprecise to establish equivalence, and potential ototoxicity means agent choice should remain individualised.

*All authors have reviewed and approved the final version of the manuscript.*

## 1. Introduction

Otomycosis, or fungal otitis externa, is a superficial mycotic infection of the external auditory canal caused predominantly by *Aspergillus* species—most notably the *Aspergillus niger* complex—and by *Candida* species, with the relative contribution of each genus varying by geography and by the diagnostic method used.[1] Molecular identification studies have shown that the causative-organism spectrum is broader than culture alone suggests, encompassing several cryptic *Aspergillus* species and non-*albicans Candida* with heterogeneous antifungal susceptibility.[2] These organisms colonise a warm, dark and frequently humid canal, and the resulting itching, otorrhoea, aural fullness and hearing impairment make otomycosis one of the more common reasons for otological consultation worldwide.

The burden of otomycosis is unevenly distributed. Reported prevalence among patients with otological complaints ranges from roughly 9% to 30% globally and is consistently higher in warm, humid regions, where recent hospital-based epidemiological series from tropical and subtropical Africa, the Middle East and Asia describe otomycosis as a substantial share of ear-nose-throat outpatient activity.[3,4] Facility-level data confirm that the condition affects all ages, with distinctive clinical and pathogen patterns in children, and that *Aspergillus* predominates in most hot-climate series.[5-7] The environmental dependence is not merely anecdotal: a single-centre time-series analysis has linked outpatient visits for fungal otitis externa directly to relative humidity and precipitation, providing quantitative support for the long-held clinical impression that sustained heat and moisture drive disease incidence.[8]

A cluster of host and behavioural risk factors compounds this climatic predisposition. Frequent ear self-manipulation, water exposure from bathing or swimming, cerumen disruption, immunosuppression and the widespread empirical use of topical antibiotic and corticosteroid drops all increase susceptibility, and case–control data identify these exposures as independent correlates of infection.[9] Poorly controlled or undiagnosed diabetes mellitus is a well-documented driver of recurrent and treatment-refractory disease, and a history of non-suppurative middle-ear surgery further raises the risk, underscoring that otomycosis frequently arises on a background of altered canal anatomy or immunity rather than in isolation.[10,11]

The mycological and micro-environmental context of tropical disease may itself shape how well individual agents perform. The *Aspergillus niger* complex produces dense, keratinophilic hyphal mats and melanised conidia and readily forms polymicrobial biofilms in the canal, structures that impede topical drug penetration and favour persistence.[12] Susceptibility surveillance from hot-climate regions shows non-negligible rates of reduced azole susceptibility among *Aspergillus* section Nigri isolates, so the assumption that any azole will reliably clear local strains cannot be taken for granted.[13] In parallel, non-*albicans Candida* with intrinsic or acquired drug resistance are increasingly reported from tropical tertiary centres, and at the severe end of the spectrum invasive or malignant fungal otitis externa illustrates the clinical stakes of inadequate eradication.[14,15]

A wide range of topical agents is used against this backdrop, including azoles (clotrimazole, ketoconazole, miconazole, econazole, eberconazole), polyenes (nystatin), allylamines (terbinafine), thiocarbamates (tolnaftate) and antiseptic or acidifying agents traditionally favoured for their low cost and availability (acetic acid, boric acid, povidone-iodine, gentian violet), often combined with meticulous aural toilet or, in some protocols, ear-canal lavage.[16] Yet the comparative evidence base remains fragmented and mostly composed of small single trials. A recent pooled analysis of two randomised trials of clotrimazole otic solution reported cure rates broadly in line with the widely cited global average of roughly three-quarters of treated ears, with no single agent established as clearly superior to the others.[17] Newer candidate therapies—including voriconazole ear drops and silver-nitrate applications—continue to be tested against clotrimazole in head-to-head randomised trials, reflecting persistent uncertainty about the optimal topical agent.[18,19]

Crucially, no synthesis has examined comparative efficacy specifically within a tropical, high-humidity epidemiological and mycological context, even though the causative-organism distribution, environmental drivers and prescribing practices in these regions may differ materially from those of temperate-climate populations. This is a substantive gap because a climate-specific answer—rather than a climate-averaged one—is what clinicians in the tropics actually need when choosing between an azole and a cheaper antiseptic. The novelty of the present work is therefore threefold: it is, to our knowledge, the first quantitative synthesis to restrict the evidence to comparative trials conducted in tropical and subtropical countries; it pre-specifies and formally pools the clinically pertinent povidone-iodine-versus-clotrimazole comparison using small-sample-robust random-effects inference (HKSJ intervals, a prediction interval and leave-one-out sensitivity analysis); and it explicitly integrates efficacy with the ototoxicity profile of each agent class, which prior efficacy-only syntheses have largely neglected. Accordingly, the aim of this study was to identify comparative clinical studies of topical antifungal and antiseptic agents for otomycosis conducted in tropical and subtropical climates, to quantify and compare their complete-cure rates—with the povidone-iodine-versus-clotrimazole contrast as the primary comparison and Southeast Asia as a pre-specified region of interest—and to appraise the certainty and safety implications of the resulting evidence.

## 2. Methods

### *2.1 Protocol and registration*

The review was conducted according to a protocol prospectively registered on PROSPERO (CRD420261456091) and is reported in accordance with the PRISMA 2020 statement.[20] The review question was framed with the PICOS structure: population—patients with otomycosis in tropical or subtropical countries (Köppen–Geiger groups A, Cfa and Cwa); intervention and comparator—any topical antifungal or antiseptic/acidifying agent versus another such agent, a different formulation, placebo, or ear cleaning alone; outcomes—complete clinical resolution and/or mycological eradication; and study designs—randomised controlled trials and non-randomised comparative clinical studies. Any amendments to the registered protocol are documented and reflected in the framing of the analysis.

### *2.2 Information sources and search*

MEDLINE (via PubMed) was searched using controlled vocabulary and free-text terms combining otomycosis and fungal otitis externa with topical antifungal and antiseptic agents (clotrimazole, ketoconazole, miconazole, tolnaftate, nystatin, terbinafine, boric acid, acetic acid and povidone-iodine) and comparative-study terms, supplemented by backward citation screening of the retrieved reports and relevant reviews. The registered protocol additionally specifies Embase, Scopus, CENTRAL, Web of Science, LILACS, Indonesian and regional databases (GARUDA, Neliti and ORLI/Jurnal THT-KL) and clinical-trial registries; the scope of database coverage achieved in the present synthesis is described transparently in the Limitations, and the cautious

framing of all estimates reflects it. No language restriction was applied at screening.

### 2.3 Study selection and data extraction

Records were screened against the eligibility criteria at title/abstract and then at full-record level. Studies were eligible if they were comparative clinical studies of two or more topical treatments (or treatment versus placebo/control) for otomycosis conducted in a tropical or subtropical country and reported an extractable complete-cure, clinical-resolution or mycological-eradication outcome with per-arm numerators and denominators (or a percentage from which a numerator could be derived). Reviews, in-vitro susceptibility studies, animal models, single-arm case series, and studies without extractable per-arm outcome data were excluded. For each included study we extracted the first author, year, country, design, agents and formulations, arm sizes, cure events at the longest reported follow-up, causative organisms and follow-up duration. Event counts derived from reported percentages are flagged as such in the shared dataset.

### 2.4 Outcomes and synthesis

The primary outcome was complete cure—complete clinical resolution and/or mycological eradication—at the longest reported follow-up. Because outcome definitions varied across studies (mycological eradication, complete clinical resolution, or a graded "good response"), each study's outcome was mapped to this construct, the mapping is reported, and outcome definition was treated as a source of heterogeneity. The pre-specified primary quantitative comparison was povidone-iodine versus clotrimazole, pooled as a risk ratio (RR) of cure. Given the small number of studies (k = 4) and anticipated heterogeneity, the DerSimonian–Laird estimate of $\tau^2$ was combined with the Hartung–Knapp–Sidik–Jonkman (HKSJ) variance correction as the primary confidence interval, because the HKSJ method provides more reliable coverage than the standard approach when few studies are pooled.[21] A 95% prediction interval was computed and a leave-one-out sensitivity analysis was performed; a 0.5 continuity correction was applied to zero-adjacent cells, with a no-correction sensitivity check. Single-arm complete-cure proportions were pooled with a random-effects model on Freeman–Tukey double-arcsine-transformed proportions, and agent-level cure rates were additionally summarised as weighted means with the number of contributing arms shown. Because every remaining head-to-head comparison contained only a single study, agent-level rates are interpreted descriptively rather than as pooled comparative effects. Heterogeneity was quantified with $I^2$, $\tau^2$ and Cochran's Q. Analyses were performed in Python (NumPy and Matplotlib) and the code is shared for independent replication. Certainty of evidence was appraised using GRADE, informed by the risk-of-bias assessment.

### 2.5 Risk of bias

Risk of bias was appraised for each study using the Cochrane Risk of Bias 2 (RoB 2) tool for randomised trials and the ROBINS-I tool for the non-randomised comparative study, across their respective domains, with an overall judgement per study.[22] Domain judgements are reported per study. Small-study and publication bias were not formally tested because fewer than ten studies contributed to any single comparison, which renders funnel-plot-based methods unreliable.

## 3. Results

### 3.1 Study selection

The database search retrieved 68 records; after screening, 40 were assessed in detail and 10 comparative clinical studies (1,970 ears) conducted in eight tropical and subtropical countries—Mexico, China, Iran, Iraq, Thailand, Pakistan, Bangladesh and Nepal—met the inclusion criteria and contributed to the qualitative synthesis. Four studies comparing povidone-iodine with clotrimazole contributed to the primary pairwise meta-analysis, and 21 treatment arms contributed to the single-arm pooled-proportion analyses. The full flow of records, including reasons for exclusion, is illustrated in Figure 1.

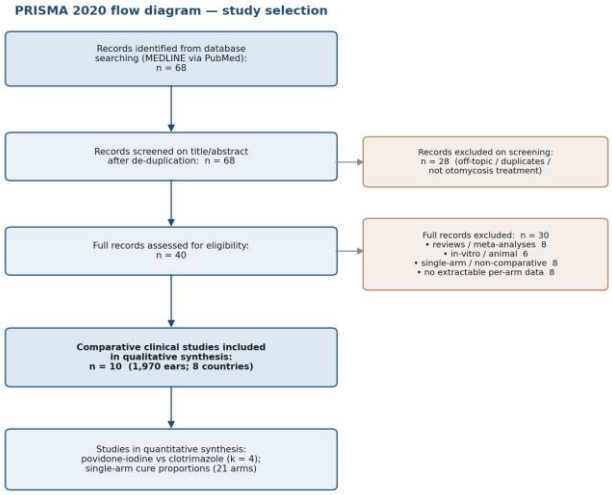


**Figure 1.** PRISMA 2020 flow diagram of study identification, screening and inclusion.

### 3.2 Characteristics of included studies

The characteristics of the ten included studies are detailed in Table 1.[23,24,25,26,27,28,29,30,31,32] All were conducted in tropical or subtropical settings; comparisons were dominated by clotrimazole, which appeared as an arm in nine of the ten studies, tested against antiseptics (povidone-iodine, salicylic acid, iodine tincture and gentian violet), other azoles (eberconazole and econazole), a polyene (nystatin), a thiocarbamate (tolnaftate) and a combination azole–corticosteroid cream. *Aspergillus* species predominated wherever causative organisms were reported. Follow-up ranged from approximately one to twelve weeks, and outcome definitions varied from mycological eradication to graded clinical response, as noted in Table 1.

**Table 1.** Characteristics of the ten included comparative studies of topical agents for otomycosis in tropical and subtropical settings. RCT = randomised controlled trial; DB = double-blind; wk = weeks; d = days.

| Study | Country | Design | Comparison | Ears | Follow-up |
|---|---|---|---|---|---|
| Jimenez-Garcia 2020 | Mexico | RCT | Clotrimazole vs tolnaftate | 48 | 1–2 wk |
| Chen 2021 | China | RCT (1:1) | Triamcinolone–econazole vs nystatin | 786 | ≥2 wk |
| Mofatteh 2018 | Iran | RCT (single-blind) | Povidone-iodine vs clotrimazole | 204 | 4–20 d |
| Numchaichanakij 2025 | Thailand | RCT (double-blind) | 10% povidone-iodine vs clotrimazole | 188 | 1–12 wk |
| Shabbir 2024 | Pakistan | RCT | Povidone-iodine gelfoam vs clotrimazole | 82 | 7–14 d |
| Jwery 2021 | Iraq | Comparative (single-blind) | Clotrimazole vs salicylic acid vs povidone-iodine | 120 | 3 wk |
| de la Paz Cota 2018 | Mexico | RCT (multicentre, DB) | Eberconazole vs clotrimazole | 190 | — |
| Mostafa 2021 | Bangladesh | RCT (open) | Clotrimazole vs econazole+triamcinolone | 102 | 2 wk |
| Dhakal 2024 | Nepal | RCT | Clotrimazole vs gentian violet | 90 | 2 wk |
| Mofatteh 2021 | Iran | RCT | Clotrimazole vs iodine tincture | 160 | 4–20 d |

### 3.3 Primary comparison: povidone-iodine versus clotrimazole

Four studies (three randomised controlled trials and one non-randomised comparative study; 528 patients) compared povidone-iodine with clotrimazole. The pooled risk ratio of complete cure was 0.86, with a wide Hartung–Knapp–Sidik–Jonkman 95% confidence interval of 0.53–1.39, as depicted in Figure 2. No statistically significant difference was detected; however, the confidence interval remains compatible with a clinically important advantage of either agent, and the 95% prediction interval of 0.29–2.58 shows that the true effect in a new tropical setting could plausibly range from a large benefit of clotrimazole to a large benefit of povidone-iodine. The absence of a detected difference should therefore not be interpreted as evidence of equivalence. Between-study heterogeneity was substantial ($I^2$ = 79%; $\tau^2$ = 0.048; Cochran's Q = 13.98, df = 3, p = 0.003), and both the pooled estimate and the prediction interval are displayed in Figure 2.

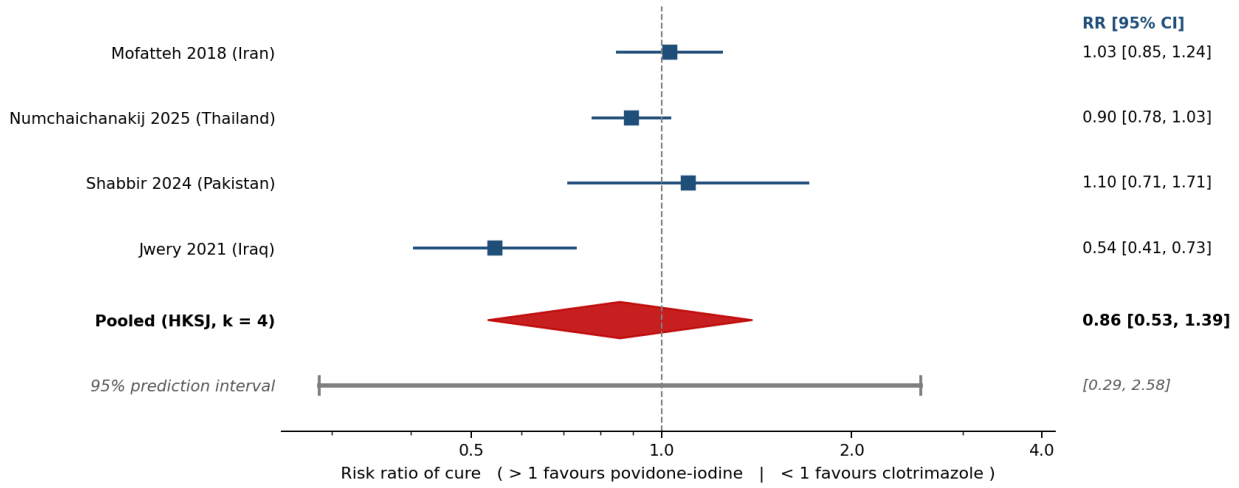


**Figure 2.** Random-effects meta-analysis of complete cure for povidone-iodine versus clotrimazole (k = 4). The red diamond is the HKSJ pooled estimate and the grey bar is the 95% prediction interval; RR \> 1 favours povidone-iodine and RR \< 1 favours clotrimazole.

A leave-one-out sensitivity analysis, presented in Figure 3, demonstrated that the entire heterogeneity was attributable to a single non-randomised study (Jwery 2021), which strongly favoured clotrimazole (RR 0.54, 95% CI 0.41–0.73).[28] When this study was omitted, the pooled RR was 0.95 (95% CI 0.85–1.06) with no residual heterogeneity ($I^2$ = 0%), indicating that among the three randomised trials povidone-iodine and clotrimazole produced near-identical cure rates. The influence of this outlying study—which also carried the highest risk of bias, as summarised in Table 3—should temper any inference of a clotrimazole advantage.

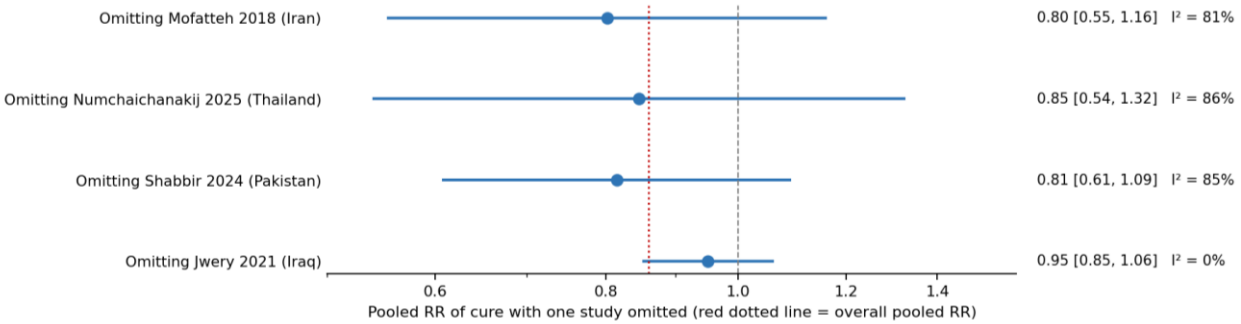


**Figure 3.** Leave-one-out sensitivity analysis for the povidone-iodine versus clotrimazole comparison. Each row shows the pooled RR when one study is omitted; the red dotted line marks the overall pooled RR.

### *3.4 Pooled cure rates by agent*

Across all 21 treatment arms (1,970 ears), the random-effects pooled complete-cure/clinical-resolution proportion (Freeman–Tukey) was 74.9% (95% CI 66.9–82.2; $I^2$ = 93%), closely matching the roughly three-quarters average eradication reported in independent global evidence and supporting the external consistency of the extracted dataset; the very high $I^2$ indicates that this figure should be read as the centre of a wide distribution rather than as a precise pooled estimate.[17] For clotrimazole specifically, the weighted-mean cure rate across nine arms was 76.4%, as detailed in Table 2, with a corresponding random-effects pooled proportion of 78.4% (95% CI 68.3–87.2; $I^2$ = 86%). The descriptive ranking of cure rates by agent is depicted in Figure 4 and quantified in Table 2: a triamcinolone–econazole combination cream (97.7%, single trial), eberconazole (82.1%) and econazole plus triamcinolone (80.4%) reported the highest rates; clotrimazole (76.4%) and nystatin (73.5%) were intermediate; the antiseptic and acidifying agents clustered between 66.3% and 72.5% (povidone-iodine 66.3%, iodine tincture 67.5%, gentian violet 71.1% and salicylic acid 72.5%); and tolnaftate reported the lowest rate (45.0%, single small trial). Because most agents are represented by a single study (k = 1), these rankings—shown in Figure 4—are hypothesis-generating and must not be read as head-to-head comparisons.

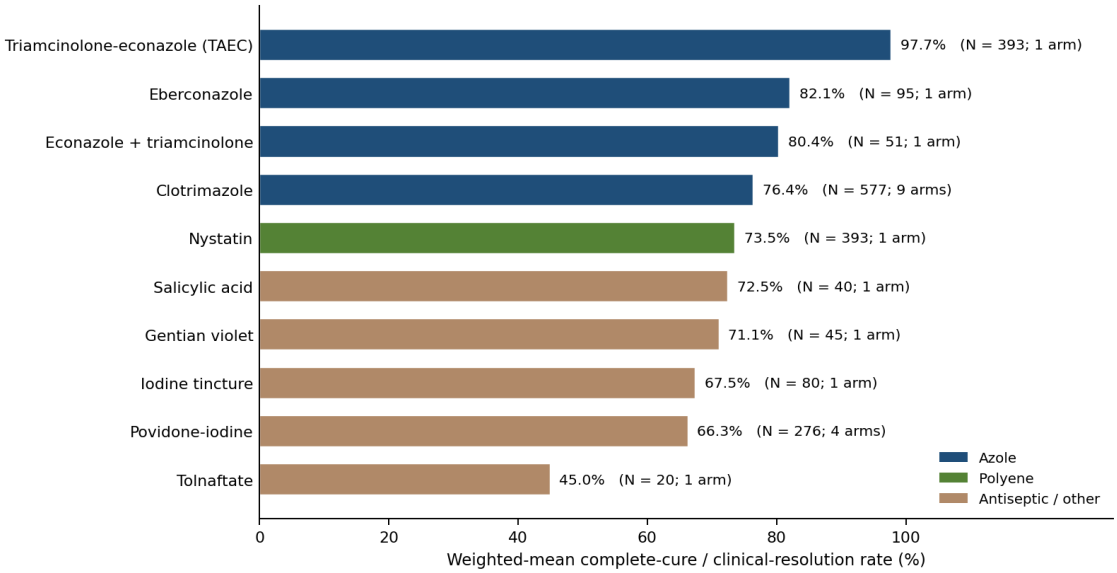


**Figure 4.** Reported complete-cure rate by topical agent across tropical and subtropical trials (descriptive single-arm rates, not head-to-head comparisons). Bars are coloured by agent class.

**Table 2.** Reported complete-cure rates by topical agent (weighted-mean single-arm rates). Agents with k = 1 are single-study estimates and are hypothesis-generating only, not pooled comparative effects.

| Agent | Arms (k) | Ears (N) | Weighted-mean cure % |
|---|---|---|---|
| Triamcinolone–econazole cream | 1 | 393 | 97.7 |
| Eberconazole | 1 | 95 | 82.1 |
| Econazole + triamcinolone | 1 | 51 | 80.4 |
| Clotrimazole | 9 | 577 | 76.4 |
| Nystatin | 1 | 393 | 73.5 |
| Salicylic acid | 1 | 40 | 72.5 |
| Gentian violet | 1 | 45 | 71.1 |
| Iodine tincture | 1 | 80 | 67.5 |
| Povidone-iodine | 4 | 276 | 66.3 |
| Tolnaftate | 1 | 20 | 45.0 |

### *3.5 Risk of bias*

Risk-of-bias judgements—RoB 2 for randomised trials and ROBINS-I for the non-randomised study—are summarised with a domain-level traffic-light layout in Table 3. Only two double-blind randomised trials (Numchaichanakij 2025 and de la Paz Cota 2018) were judged at low risk of bias overall.[26,29] Most trials raised "some concerns", chiefly from open or unclear blinding of participants and outcome assessors for subjective clinical-resolution outcomes and from unclear allocation concealment. Two trials using visibly staining or coloured agents—gentian violet and a povidone-iodine formulation—were rated at high risk because blinded outcome assessment is essentially impossible when the treatment is self-evident.[30,31] The single non-randomised comparative study (Jwery 2021), which drove the heterogeneity of the primary comparison, was rated at serious risk of bias under ROBINS-I, predominantly for uncontrolled confounding and unblinded outcome measurement, as shown in Table 3.[28] These judgements directly informed the certainty appraisal below and reinforce caution regarding the outlying result.

**Table 3.** Risk-of-bias assessment. RoB 2 domains: D1 randomisation process; D2 deviations from intended interventions (blinding); D3 missing outcome data; D4 measurement of the outcome; D5 selection of the reported result. ROBINS-I domains are mapped to the corresponding columns (D1 confounding; D2 selection/deviations; D3 missing data; D4 outcome measurement; D5 selective reporting). Green = low; amber = some concerns/moderate; red = high/serious.

| Study | Tool | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|---|
| Jimenez-Garcia 2020 | RoB 2 | Some | Some | Low | Some | Some | Some concerns |
| Chen 2021 | RoB 2 | Some | Some | Low | Some | Some | Some concerns |
| Mofatteh 2018 | RoB 2 | Some | Some | Low | Some | Some | Some concerns |
| Numchaichanakij 2025 | RoB 2 | Low | Low | Low | Low | Low | Low |
| Shabbir 2024 | RoB 2 | Some | High | Low | High | Some | High |
| de la Paz Cota 2018 | RoB 2 | Low | Low | Low | Low | Low | Low |
| Mostafa 2021 | RoB 2 | Some | Some | Low | Some | Some | Some concerns |
| Dhakal 2024 | RoB 2 | Some | High | Low | High | Some | High |
| Mofatteh 2021 | RoB 2 | Some | Some | Low | Some | Some | Some concerns |
| Jwery 2021 | ROBINS-I | Serious | Moderate | Low | Serious | Moderate | Serious |

### *3.6 Other head-to-head comparisons*

Individual trials that could not be pooled provided the following direct comparisons, each consistent with the agent-level rates in Table 2. Clotrimazole was superior to tolnaftate (75.0% versus 45.0% at one week; Mexico); the triamcinolone–econazole cream was superior to nystatin (97.7% versus 73.5%; China); and clotrimazole was statistically comparable to eberconazole (83.5% versus 82.1%; Mexico), to econazole plus triamcinolone (88.2% versus 80.4%; Bangladesh) and to gentian violet (86.7% versus 71.1%; Nepal), while performing marginally below iodine tincture (62.5% versus 67.5%; Iran). In the three-arm Iraqi study, clotrimazole (97.5%) outperformed both salicylic acid (72.5%) and povidone-iodine (52.5%). Taken together, azoles consistently matched or exceeded antiseptic and older antifungal comparators, whereas differences between azoles and modern antiseptics such as povidone-iodine were small and inconsistent in direction.

### 3.7 Certainty of evidence

The GRADE certainty of evidence for the povidone-iodine-versus-clotrimazole comparison was rated low to very low. It was downgraded for risk of bias (most trials at "some concerns" and the influential study at serious risk, as shown in Table 3), for inconsistency ($I^2$ = 79%, driven by that single study, as demonstrated in Figure 3) and for imprecision (a wide HKSJ interval and a prediction interval spanning a large benefit of either agent, as shown in Figure 2). The single-study, agent-level cure rates in Table 2 constitute very-low-certainty descriptive evidence owing to non-randomised between-study comparison, single-study fragility and considerable heterogeneity, and were not used to grade comparative effects.

## 4. Discussion

In this synthesis restricted to tropical and subtropical settings, topical antifungal and antiseptic agents achieved a moderate random-effects pooled complete-cure rate of 74.9%, closely mirroring independent global estimates and consistent with the view that no single topical agent is clearly superior.[17] For the pre-specified primary comparison—povidone-iodine versus clotrimazole—no significant difference was detected, but we deliberately avoid the language of "equivalence": the HKSJ confidence interval (0.53–1.39) and the prediction interval (0.29–2.58) shown in Figure 2 are wide enough to remain compatible with a clinically important advantage of either agent. Importantly, the leave-one-out analysis in Figure 3 showed that the observed heterogeneity and the numerical direction towards clotrimazole were driven entirely by a single non-randomised study at serious risk of bias; among the three randomised trials the two agents were near-identical (RR 0.95, $I^2$ = 0%). Povidone-iodine therefore remains a plausible low-cost option where azole access is constrained, but the data neither confirm equivalence nor justify displacing clotrimazole.

These results are concordant with recent randomised and pooled trial evidence, in which clotrimazole and comparator regimens achieve broadly similar cure rates without a consistent winner, and in which the average proportion cured hovers around three-quarters of treated ears.[16,17] Our contribution is to show that this convergence and heterogeneity persist when the evidence is deliberately confined to tropical and subtropical populations, where *Aspergillus*-predominant disease and high-humidity conditions might plausibly have altered comparative efficacy but empirically did not produce a distinct signal. The consistent superiority of clotrimazole over tolnaftate, and of the combination azole–corticosteroid cream over nystatin (Table 2, Figure 4), suggests that agent class and formulation matter more than the broad antifungal-versus-antiseptic dichotomy.

A striking finding of both this review and its protocol-stage scoping is the near-absence of Indonesian and, more broadly, Southeast Asian comparative trials indexed internationally: none of the ten included studies (Table 1) originated from Indonesia despite the country's endemic burden of otomycosis. This confirms a genuine evidence gap and supports the pre-specified rationale for the wider tropical scope of the registered review (PROSPERO CRD420261456091). Adequately powered Indonesian randomised trials with standardised, mycologically confirmed cure definitions are a clear research priority.

### 4.1 Tropical mycology and comparative pharmacology

A climate-restricted synthesis is justified only if the tropical mycological and environmental context could plausibly modify comparative efficacy, and several mechanisms make this plausible. Otomycosis in hot, humid regions is disproportionately caused by the *Aspergillus niger* complex, whose dense hyphal mats and melanised conidia form a physical and biochemical barrier that impedes topical drug penetration and favours mechanical debridement as a co-determinant of cure.[12] Persistent high ambient humidity, which is quantitatively linked to disease incidence, promotes re-inoculation and biofilm re-formation, and these processes can blunt the apparent efficacy of any short-course agent and compress between-agent differences—one explanation for the convergence of azole and antiseptic cure rates observed here.[8,12] Pharmacologically, azoles act largely fungistatically by inhibiting ergosterol synthesis, whereas acidifying antiseptics act through rapid, non-specific microbicidal and pH-lowering effects that are relatively organism-agnostic; in an *Aspergillus*-dominant, biofilm-prone niche these differing mechanisms may yield a similar net cure. Emerging susceptibility data reinforce this nuance: reduced azole susceptibility among section Nigri isolates and the correlation between in-vitro minimum inhibitory concentrations and clinical response suggest that azole superiority cannot be assumed and should ideally be guided by local surveillance.[13,33] The relatively high proportion of non-*albicans* *Candida* with variable azole susceptibility reported from some tropical series argues in the same direction.[14] These considerations reframe the observed "no detected difference" as biologically unsurprising rather than merely a null result of an underpowered analysis. They also motivate the active pipeline of alternative and adjunctive approaches now under study—including plant-derived essential oils with anti-*Candida* activity and novel synergistic drug-delivery vesicles designed to improve penetration of the fungal biofilm—which may eventually widen the currently narrow therapeutic gap between agents.[34,35]

### 4.2 Safety and ototoxicity

Efficacy cannot be considered in isolation from safety, which is particularly salient for intratympanic exposure. Reported adverse effects across the included trials were generally mild and local, comprising otalgia, pruritus and transient burning.

However, several agents in this evidence base carry real or theoretical cochleovestibular toxicity that becomes clinically important when the tympanic membrane is not intact—a common scenario in chronic tropical otomycosis. Boric and acetic acid preparations, gentian violet and iodine-containing antiseptics have all been associated with ototoxicity or mucosal irritation in the presence of perforation, and alcohol-based vehicles compound this risk; this is precisely why the two coloured or staining agents in this dataset were also the least amenable to blinded assessment (Table 3). Clotrimazole and other azoles are generally regarded as free of ototoxic potential in standard formulations, and the deliberate evaluation of azole safety in the specific setting of tympanic-membrane perforation is an encouraging direction that antiseptic agents have not matched.[36] Any recommendation to use low-cost antiseptics as first-line therapy must therefore be conditioned on documented tympanic-membrane integrity, and future studies should routinely report perforation status and audiometric safety outcomes—data that were largely absent from the included trials and that constitute an important evidence gap.

### *4.3 Clinical implications*

For pragmatic tropical ENT practice, three points follow. First, meticulous aural toilet and microscopic debridement remain the single most important therapeutic step and a likely common denominator of the high cure rates seen across agents in Table 2, regardless of the specific drug applied. Second, a topical azole such as clotrimazole is a reasonable default first-line agent given its efficacy, tolerability and absence of ototoxicity, while povidone-iodine or acidifying agents are defensible, inexpensive alternatives where the tympanic membrane is intact and azole access is limited. Third, therapy should be organism-informed where feasible—azoles for *Aspergillus*-predominant disease and, for *Candida*, after considering local non-*albicans* susceptibility—and should include an adequate treatment duration and follow-up to detect the recurrence that is characteristic of humid climates. Practical adherence also matters: recent randomised evidence indicates that supervised or physician-applied topical therapy can influence outcomes relative to self-application, a consideration directly relevant to resource-variable tropical settings.[37] These implications are offered as cautious, evidence-informed guidance rather than as prescriptive recommendations, given the low certainty of the underlying data.

### *4.4 Strengths and limitations*

The strengths of this work include a prospectively registered protocol, a clinically important pre-specified comparison, a transparent and fully reproducible analysis with shared data and code, the use of small-sample-robust inference (HKSJ intervals, prediction intervals and leave-one-out sensitivity analysis), a structured domain-level risk-of-bias assessment (Table 3), and external consistency with independent global estimates. Several limitations must nonetheless be emphasised. First, database coverage was concentrated on MEDLINE/PubMed, whereas the registered protocol specifies additional international and Indonesian or regional databases; further eligible studies almost certainly exist and would refine the estimates, so the present findings are best interpreted as a focused synthesis of the internationally indexed comparative literature. Second, several event counts were derived from reported percentages rather than verbatim numerators, and these are flagged in the shared dataset. Third, outcome definitions (mycological eradication versus graded clinical response) and follow-up windows (approximately one to twelve weeks) were heterogeneous, the unit of analysis (ears versus patients) varied across studies, and single-study agent rates cannot support causal comparisons. Fourth, the primary quantitative comparison rested on only four studies, one of which was non-randomised and dominated the heterogeneity. Accordingly, all comparative estimates should be read as low-to-very-low-certainty evidence that structures and quantifies the current literature while awaiting the broader, multi-database evidence anticipated by the registered protocol.

### *4.5 Implications for future research*

The gaps exposed by this synthesis translate into a concrete research agenda. Priority should be given to adequately powered, double-blind randomised trials conducted in tropical and subtropical populations—Indonesia foremost among them—that adopt a single, mycologically confirmed definition of cure, report per-ear and per-patient denominators separately, and record tympanic-membrane status and audiometric safety outcomes as standard endpoints rather than as afterthoughts. Trials should stratify or pre-specify subgroups by causative genus, because the pharmacological arguments above predict that azole-versus-antiseptic differences, if they exist, are most likely to emerge in *Candida*-predominant or azole-non-susceptible *Aspergillus* disease rather than in aggregate.[13,14,33] Embedding local antifungal-susceptibility surveillance within such trials would allow efficacy to be interpreted against the actual resistance landscape rather than an assumed one. Equally, head-to-head evaluation of emerging agents and delivery systems—voriconazole otic preparations, silver-nitrate applications, essential-oil adjuncts and biofilm-penetrating vesicular carriers—should be benchmarked against clotrimazole and against meticulous aural toilet alone, so that any incremental benefit is weighed against cost, availability and ototoxic risk.[18,19,34,35] Finally, completion of the broader multi-database evidence base anticipated by the registered protocol, combined with individual-participant-data pooling where feasible, would substantially sharpen the imprecise estimates reported here and could resolve whether the apparent convergence of agents is real or an artefact of underpowered, heterogeneous trials.

## 5. Conclusion

In tropical and subtropical settings, topical azoles—particularly clotrimazole—and low-cost antiseptics such as povidone-iodine and acidifying agents appear to achieve broadly similar, moderate cure rates for otomycosis, with no agent demonstrating clear superiority. The evidence is, however, heterogeneous, of low-to-very-low certainty, and too imprecise to establish equivalence, because a clinically important difference in either direction cannot be excluded. Povidone-iodine and acidifying antiseptics are reasonable, economical options where the tympanic membrane is intact and azole access is limited, but their potential ototoxicity means that agent choice should remain individualised, and clotrimazole—efficacious and non-ototoxic—remains a sound default. The conspicuous lack of Indonesian and Southeast Asian trials, the absence of reported safety and perforation data, and heterogeneous outcome definitions together define a clear agenda for adequately powered, standardised regional randomised trials.

## Declarations

**Registration:** PROSPERO CRD420261456091.

**Funding:** No specific or external funding.

**Competing interests:** None declared.

**Data availability:** The extracted dataset and analysis code are available in the study's supplementary files.

**Author contributions:** RH conceived and designed the review, supervised the analysis and drafted the manuscript (guarantor); OAP and AAR contributed to screening, data extraction and critical revision. All authors approved the final version.

## References

1. Roohi B, Nemati S, Alipour A, et al. Otomycosis: the foremost aetiological agent causing otitis externa and the antifungal susceptibility pattern in North-Western Iran. Mycoses. 2023;66(2):87–97. doi:10.1111/myc.13532.
2. Kiakojuri K, Mahdavi Omran S, Roodgari S, et al. Molecular identification and antifungal susceptibility of yeasts and molds isolated from patients with otomycosis. Mycopathologia. 2021;186(2):245–257. doi:10.1007/s11046-021-00537-1.
3. Diop A, Younes H, Diop PS, et al. Epidemiological profile of otomycosis at the Peace Hospital of Ziguinchor (Senegal). J Fungi (Basel). 2025;11(3):218. doi:10.3390/jof11030218.
4. Wang Q, Xu D, Li Y, et al. Otomycosis in Southern China: a retrospective analysis of clinical presentation, otoendoscopic features, and causative pathogens. Mycopathologia. 2025;191(1):15. doi:10.1007/s11046-025-01036-3.
5. Du J, Zhan X, Liu Y, et al. Epidemiological characteristics and trends in the diagnosis and treatment of fungal otitis externa in children. Transl Pediatr. 2025;14(7):1489–1497. doi:10.21037/tp-2025-169.
6. Abraham ZS. Aetiological profile, clinical features and risk factors for otomycosis in Dar es Salaam, Tanzania: a cross-sectional study. Indian J Otolaryngol Head Neck Surg. 2024;76(5):4133–4137. doi:10.1007/s12070-024-04800-x.
7. Asoegwu CN, Oladele RO, Kanu OO, et al. Clinical and microbiological profile of otomycosis in Lagos, Nigeria. Niger Postgrad Med J. 2023;30(2):132–136. doi:10.4103/npmj.npmj_9_23.
8. Meng X, Cai M. Relative humidity, precipitation, and outpatient visits for clinically diagnosed fungal otitis externa: a single-center time-series study in Wuxi, eastern China. Front Public Health. 2026;14:1859702. doi:10.3389/fpubh.2026.1859702.
9. Liu P, Ye C, Zhuang L, et al. Clinical features and risk factors of otomycosis: a case-control study. Ear Nose Throat J. 2026. doi:10.1177/01455613251413977.
10. Gill N, Meena V. Recurrent otomycosis in patients with undiagnosed diabetes mellitus: a clinical analysis. J Laryngol Otol. 2026;140(2):177–182. doi:10.1017/S0022215125104039.
11. Gul F, Kocak O, Ozturk A, et al. Otomycosis risk after non-suppurative middle ear surgery. Braz J Otorhinolaryngol. 2025;91(2):101552. doi:10.1016/j.bjorl.2024.101552.
12. Al-Oebady MAH. Study of the antagonistic relationship between gene-expression biofilm of *Aspergillus niger* and *Staphylococcus aureus* that cause otomycosis. Curr Med Mycol. 2024;10:e2024.345248. doi:10.22034/cmm.2024.345248.1586.
13. Asadzadeh M, Khan Z, Ahmad S, et al. Prevalence of *Aspergillus* section Nigri complex species isolated from clinical specimens in Kuwait and their susceptibility to antifungal drugs. J Fungi (Basel). 2026;12(6):430. doi:10.3390/jof12060430.
14. Alam MM, Biplob JA, Sathi FA, et al. Ear infections by non-*albicans Candida* species with isolation of rare drug-resistant species in a tertiary care hospital of Bangladesh. Mymensingh Med J. 2023;32(3):644–648.
15. Halwani C, Mtibaa L, Hamdi ME, et al. A retrospective study of 43 cases of fungal malignant external otitis. Pan Afr Med J. 2022;41:287. doi:10.11604/pamj.2022.41.287.29585.
16. Zhang J, Du Y, Tang L, et al. Ear-canal lavage for curing noninvasive otomycosis: a randomized controlled trial. Eur Arch Otorhinolaryngol. 2025;282(9):4645–4652. doi:10.1007/s00405-025-09418-5.
17. Ansley JF, Bernal-Sprekelsen M, Butehorn HF, et al. Pooled analysis of 2 randomized clinical trials to evaluate the efficacy and safety of clotrimazole 1% otic solution for the treatment of otomycosis in adults. J Otolaryngol Head Neck Surg. 2025;54:19160216251330629. doi:10.1177/19160216251330629.
18. Qian S, Tan G, Tan H, et al. A single-center, randomized, double-blinded, placebo-controlled clinical study on the efficacy and safety of voriconazole ear drops in the treatment of otomycosis. Am J Otolaryngol. 2026;47(1):104792. doi:10.1016/j.amjoto.2026.104792.
19. Tantawy RF, Elsharkawy AS, Hashem H, et al. The effect of silver nitrate versus clotrimazole in treatment of otomycosis. Eur Arch Otorhinolaryngol. 2026. doi:10.1007/s00405-026-10162-7.

20. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71.
21. IntHout J, Ioannidis JPA, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random-effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol. 2014;14:25. doi:10.1186/1471-2288-14-25.
22. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. doi:10.1136/bmj.l4898.
23. Jimenez-Garcia L, Celis-Aguilar E, Díaz-Pavón G, et al. Efficacy of topical clotrimazole vs. topical tolnaftate in the treatment of otomycosis: a randomized controlled clinical trial. Braz J Otorhinolaryngol. 2020;86(3):300–307. doi:10.1016/j.bjorl.2018.12.007.
24. Chen Q, Chu H, Tao Y, et al. A comparison of triamcinolone acetonide econazole cream and nystatin suspension in treatment of otomycosis. Laryngoscope. 2021;131(5):E1640–E1646. doi:10.1002/lary.29190.
25. Mofatteh MR, Naseripour Yazdi Z, Yousefi M, et al. Comparison of the recovery rate of otomycosis using betadine and clotrimazole topical treatment. Braz J Otorhinolaryngol. 2018;84(4):404–409. doi:10.1016/j.bjorl.2017.04.004.
26. Numchaichanakij P, Kreesaeng P. Comparison of efficacy in the treatment of otomycosis using 10% povidone-iodine and clotrimazole solution: a randomized, double-blind controlled trial. Int Arch Otorhinolaryngol. 2025;29(3):1–4. doi:10.1055/s-0045-1810001.
27. Shabbir Z, Ashfaq AH, Arshad M, et al. Efficacy of pyodine-soaked gelfoam vs single topical application of clotrimazole in treatment of otomycosis: a randomized controlled clinical trial. Indian J Otolaryngol Head Neck Surg. 2024;76(6):5091–5097. doi:10.1007/s12070-024-05076-x.
28. Jwery AK. Various topical antifungal agents in otomycosis, which is the best? J Pak Med Assoc. 2021;71(Suppl 8):S32–S34.
29. de la Paz Cota BR, Cepero Vega PP, Matus Navarrete JJ, et al. Efficacy and safety of eberconazole 1% otic solution compared to clotrimazole 1% solution in patients with otomycosis. Am J Otolaryngol. 2018;39(3):307–312. doi:10.1016/j.amjoto.2018.03.017.
30. Mostafa MG, Ahmed S, Islam MR, et al. Efficacy of clotrimazole 1% solution compared to econazole nitrate 1% + triamcinolone acetonide 0.1% cream in patients with otomycosis. Mymensingh Med J. 2021;30(3):638–643.
31. Dhakal S, Bagale G, Nepal A, et al. Comparison of recovery rate of otomycosis using one-percent gentian violet and one-percent clotrimazole topical treatment. J Nepal Health Res Counc. 2024;22(2):269–273. doi:10.33314/jnhrc.v22i02.4885.
32. Mofatteh MR, Ahi Fersheh M, Nikoomanesh F, et al. Comparing the therapy of otomycosis using clotrimazole with iodine tincture: a clinical trial. Iran J Otorhinolaryngol. 2021;33(117):229–235. doi:10.22038/ijorl.2021.51647.2751.
33. Sun Y, Liu D. Correlation between MIC of econazole nitrate and clinical response in otomycosis. Front Cell Infect Microbiol. 2026;16:1820764. doi:10.3389/fcimb.2026.1820764.
34. Stojanović-Radić Z, Stojković O, Radulović N, et al. Antifungal activity of *Thymus vulgaris* L. essential oil against *Candida* species causing otomycosis. Chem Biodivers. 2025;22(12):e01145. doi:10.1002/cbdv.202501145.
35. Fahmy AM, Saher O, Attia H, et al. Harnessing novel tetra-synergistic bilosomes for effective otomycosis management: integrated in-vitro, microbiological and in-vivo studies. AAPS PharmSciTech. 2026;27(3):101. doi:10.1208/s12249-026-03342-5.
36. Jin M, Zhao Y, Dong Z, et al. Evaluation of the safety of 1% voriconazole ear drops for the treatment of tympanic-membrane-perforation-associated suppurative otomycosis. Pak J Pharm Sci. 2025;38(5):1775–1783. doi:10.36721/PJPS.2025.38.5.REG.14677.1.
37. Ye C, Hong Y, Cai Y. Comparison of the efficacy of patient self-application versus physician application of triamcinolone acetonide econazole cream in the treatment of otomycosis: a randomized open-label controlled trial. J Laryngol Otol. 2025. doi:10.1017/S0022215125000271.