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Original Article

Talaromyces marneffei, *Coccidioides* species, and *Paracoccidioides* species—a systematic review to inform the World Health Organization priority list of fungal pathogens

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Abstract

The World Health Organization, in response to the growing burden of fungal disease, established a process to develop a fungal pathogen priority list. This systematic review aimed to evaluate the epidemiology and impact of infections caused by *Talaromyces marneffei, Coccidioides* species, and *Paracoccidioides* species. PubMed and Web of Sciences databases were searched to identify studies published between 1 January 2011 and 23 February 2021 reporting on mortality, complications and sequelae, antifungal susceptibility, preventability, annual incidence, and trends. Overall, 25, 17, and 6 articles were included for *T. marneffei, Coccidioides* spp. and *Paracoccidioides* spp., respectively. Mortality rates were high in those with invasive talaromycosis and paracoccidioidomycosis (up to 21% and 22.7%, respectively). Hospitalization was frequent in those with coccidioidomycosis (up to 84%), and while the duration was short (mean/median 3–7 days), readmission was common (38%). Reduced susceptibility to fluconazole and echinocandins was observed for *T. marneffei* and *Coccidioides* spp., whereas >88% of *T. marneffei* isolates had minimum inhibitory concentration values ≤0.015 μg/ml for itraconazole, posaconazole, and voriconazole. Risk factors for mortality in those with talaromycosis included low CD4 counts (odds ratio 2.90 when CD4 count <200 cells/μl compared with 24.26 when CD4 count <50 cells/μl). Outbreaks of coccidioidomycosis and paracoccidioidomycosis were associated with construction work (relative risk 4.4–210.6 and 5.7-times increase, respectively). In the United States of America, cases of coccidioidomycosis increased between 2014 and 2017 (from 8232 to 14 364/year). National and global surveillance as well as more detailed studies to better define sequelae, risk factors, outcomes, global distribution, and trends are required.

Key words: *Talaromyces marneffei, Penicillium marneffei, Coccidioides, Paracoccidioides*, talaromycosis, penicilliosis, coccidioidomycosis, paracoccidioidomycosis, invasive fungal disease, mortality, epidemiology, antifungal resistance.

Introduction

Talaromyces marneffei, *Coccidioides* species (spp.), and *Paracoccidioides* spp. are endemic fungi. While having distinct characteristics, they also have commonalities, including the ability to cause disease in both healthy and immunocompromised hosts, increasing incidence, geographical expansion, and significant morbidity and/or mortality.[1,2]

Talaromyces marneffei (formerly *Penicillium marneffei*) is a thermally dimorphic fungus endemic to northern Thailand, Vietnam, Myanmar, Hong Kong, Taiwan, southern China, and north-eastern India. The bamboo rat (*Rhizomys sinensis*) is the natural reservoir; however, human infection is not linked to its direct exposure or consumption. Occupational exposure to crops and livestock is a risk factor, and talaromycosis incidence increases 30%–50% in the rainy season.[3–6] The lungs are the primary portal of entry. It is likely that the humidity in the rainy season creates favorable conditions for fungal growth, and aerosolized particles are inhaled when the ecological niche is disturbed. *Talaromyces marneffei* can disseminate to other organs via lymphatic and hematogenous spread.[7–9] Pulmonary and localized disease occur in immunocompetent patients, and disseminated disease occurs most commonly in those who are immunocompromised. Human immunodeficiency virus (HIV) is a major risk factor for talaromycosis accounting for up to 16% of all HIV-associated hospital admissions in Southeast Asia.[1,5,10,11] More recently, talaromycosis has been increasingly described in non-HIV patients (those with primary immunodeficiencies, auto-immune diseases, or hematological malignancies) who reside in or have previously traveled to Southeast Asia.[1]

Coccidioides spp. are dimorphic fungi found in the soil of arid and semi-arid regions in the southwest of the USA, Mexico, and parts of South and Central America (Argentina, Bolivia, Brazil, Colombia, Paraguay, Venezuela, Guatemala, and Honduras).[12,13] Coccidioidomycosis, caused by *Coccidioides immitis* and *Coccidioides posadasii,* is now a notifiable (voluntary) disease to the National Notifiable Disease Surveillance System of the Centers for Disease Control. In addition, it is a requirement to report it to the public health departments of 27 jurisdictions in the USA.[14] In Arizona, the incidence has increased from 84.4/100 000 population to 144.1/100 000 between 2014 and 2019.[14] While mandatory reporting has contributed to the increasing numbers, other factors such as environmental changes, population growth, and increased awareness have also contributed. Several outbreaks in California and Utah point to an extension of northward and with whole genome sequencing, local acquisition has been identified as far north as Washington State.[15–17] The reasons for the geographical expansion are largely unknown, but climate change may play a role.[18] Risk factors for coccidioidomycosis include being an African American prison inmate and failure to screen prior to transplantation or commencing tumor necrosis factor-α (TNF-α) inhibitors. Occupational dust exposure while constructing solar farms has more recently been recognized as a risk factor. Inhalation is the primary mode of acquisition. Symptoms only occur in 40% of those infected and are indistinguishable from those of other respiratory infections (cough, fever, dyspnea, and fatigue). As a result, misdiagnosis is common resulting in delays in appropriate therapy. Infection is mostly self-limiting, but some people can develop pneumonia lasting up to 6 weeks, requiring antifungal therapy. Importantly, a small proportion develops life-threatening pulmonary or disseminated diseases.[14,19] Mortality rates of 30% in those with coccidioidal meningitis are still reported despite antifungal treatment.[20]

Paracoccidioides spp. are thermally dimorphic fungi, endemic to Central and South America, and composed of at least five species; *P. brasiliensis sensu stricto*, *P. americana, P. restrepiensis, P. venezuelensis*, and *P. lutzii*.[21–24] While there is clear geographical overlap, *Paracoccidioides* spp. show little genetic exchange.[22,23,25,26] Brazil has the highest number of cases of paracoccidioidomycosis (80%).[27] The major risk is occupational exposure to soil.[27] With increasing deforestation of land for agriculture in northern and central parts of Brazil, the incidence of paracoccidioidomycosis has increased, whereas with increased mechanization of agriculture in southern Brazil, the numbers have decreased.[27–32] Other risk factors, particularly for the chronic form, include smoking (14-fold higher risk than non-smokers) and alcohol (3.5-fold), while estrogen may have a protective effect.[27],33Paracoccidioidomycosis is also primarily acquired by inhalation. Only 1%–2% will develop symptomatic infection.[34] Of those that develop clinical manifestations, 10%–25% will present as the acute/subacute form, characterized by rapid progression of skin lesions, lymphadenopathy, hepatosplenomegaly, and then fevers, suppuration, and anorexia,[35–37] while the remaining cases (75%–95%) will develop chronic disease many years later, usually after the third

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decade of life. Chronic paracoccidioidomycosis mainly affects the lungs (65%–90%), mucous membranes, skin, and eventually the adrenal glands and the central nervous system.[27,34,38–40] Cough, dyspnea, and sputum are the most common manifestations of chronic paracoccidioidomycosis, although granulomatous oral ulceration occurs in up to 59.6%.[41] Paracoccidioidomycosis is uncommon in the immunocompromised. However, when it occurs, it is usually as mixed forms, and it rarely causes significant impairment. Mortality is low, but morbidity, secondary fibrosis, and organ dysfunction can occur in up to 50% despite treatment.[38]

Given their emerging importance, this systematic review aims to evaluate infections due to *T. marneffei*, *Coccidioides* spp., and *Paracoccidioides* spp. against a set of criteria; mortality, inpatient care, complications and sequelae, antifungal susceptibility, preventability, annual incidence, global distribution, and emergence in the 10 years from 1 January 2011 to 23 February 2021. The generated data identified knowledge gaps for *T. marneffei*, *Coccidioides* spp., and *Paracoccidioides* spp., informing the fungal pathogen priority list of the World Health Organization (WHO).[42]

Methods

Study design

A systematic review was performed using the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Guidelines.[43]

Inclusion and exclusion criteria

Studies were included if they reported data on: (a) adults and/or pediatric populations; (b) *T. marneffei*, *Coccidioides* spp., or *Paracoccidioides* spp.; (c) at least one criterion (mortality, inpatient care, complications/sequelae, antifungal susceptibility, preventability, annual incidence, global distribution, and emergence) in the previous 10 years; (d) retrospective or prospective observational studies, randomized controlled trials (RCTs), epidemiological, or surveillance studies; and (e) were published between 1 January 2011 and 23 February 2021. Studies were excluded if they reported on/were: (a) animals or plants only; (b) bacteria, viruses, and/or parasites only; (c) other fungi or criteria only; (d) co-infection only; (e) novel antifungals in pre-clinical or early-phase trials or unlicensed antifungals only; (f) *in vitro* resistance mechanisms only; (g) case reports or conference abstracts; (h) not in English; and (i) outside the study time-frames.

Search strategy

We conducted a comprehensive search for studies published in English using the PubMed and Web of Science Core Collection databases between 1 January 2011 and 23 February 2021. On PubMed, the search was optimized using medical subject headings (MeSH) and/or keyword terms in the title/abstract for *T. marneffei*, *Coccidioides* spp., and *Paracoccidioides* spp. and each criterion. On the Web of Science, MeSH terms are not available, and therefore topic, title, or abstract searches were used. The final searches used can be found in the supplementary materials.

PubMed and related databases are underpinned by a standardized taxonomy database. Thus, using a species name as a search term retrieves articles with obsolete or updated nomenclature.[44] Hence, this search using the *Talaromyces* term retrieved articles utilizing either *Talaromyces marneffei* or *Penicillium marneffei*.

Study selection

The final search results from each database were imported into the reference manager, Endnote™, and the online systematic review software, Covidence® (Veritas Health Innovation, Australia), and duplicates were removed. The remaining articles underwent title and abstract screening based on the eligibility criteria, and no reasons were provided for excluding articles at this step. Then, full-text screening was performed to determine eligibility for inclusion and the reasons for excluding any articles recorded. The title/abstract screening and full-text screenings were performed independently by J.B. and A.D. (*T. marneffei*), H.Y.K. and A.D. (*Coccidioides* spp.), and H.Y.K. and B.N. (*Paracoccidioides* spp.) in Covidence®. Discrepancies were resolved by a third reviewer (J.W.A.). Any additional articles identified from the references of the included articles were added.

Data extraction

Data from the final set of eligible articles were extracted for each relevant criterion by one of the screening reviewers (H.Y.K.) and were independently checked for accuracy by other reviewers (A.D., J.B., A.M., and B.Mc.M.).

Risk of bias assessment

Risk of bias assessment was independently performed by two reviewers (H.Y.K. and C.O.M.) for the included studies. Risk of bias tool for randomized trials (ROB version 2) and risk of bias tool for non-randomized studies (RoBANS) were used in this assessment.[45,46] For the overall risk, using ROB 2 tool, the studies were rated low, high, or some concerns. Using RoBANS tool, the studies were rated as low, high, or unclear risk.

This systematic review was intended to inform specific criteria; therefore, we used each criterion as an outcome of the study and assessed if any bias was expected based on the study design, data collection, or analysis in that particular study. With this approach, studies classified as unclear or high overall risk were still considered for analysis.

Data synthesis

The extracted data on the outcome criteria were quantitatively (proportions [%], mean, median, range) or qualitatively analyzed depending on the amount and nature of the data.

Results

Study selection

Between 1 January 2011 and 23 February 2021, the PubMed and Web of Science databases yielded 64 and 116 articles on *T. marneffei* (Fig. 1a), 162 and 184 articles on *Coccidioides* spp. (Fig. 1b), and 137 and 199 articles on *Paracoccidioides* spp. (Fig. 1c), respectively. After excluding the duplicated and non-relevant articles, 34, 22, and 11 articles underwent full-text screening, of which 25, 17, and 6 articles on *T. marneffei*, *Coccidioides* spp., and *Paracoccidioides* spp., respectively, were deemed eligible for inclusion in the final analysis (Fig. 1a–c).

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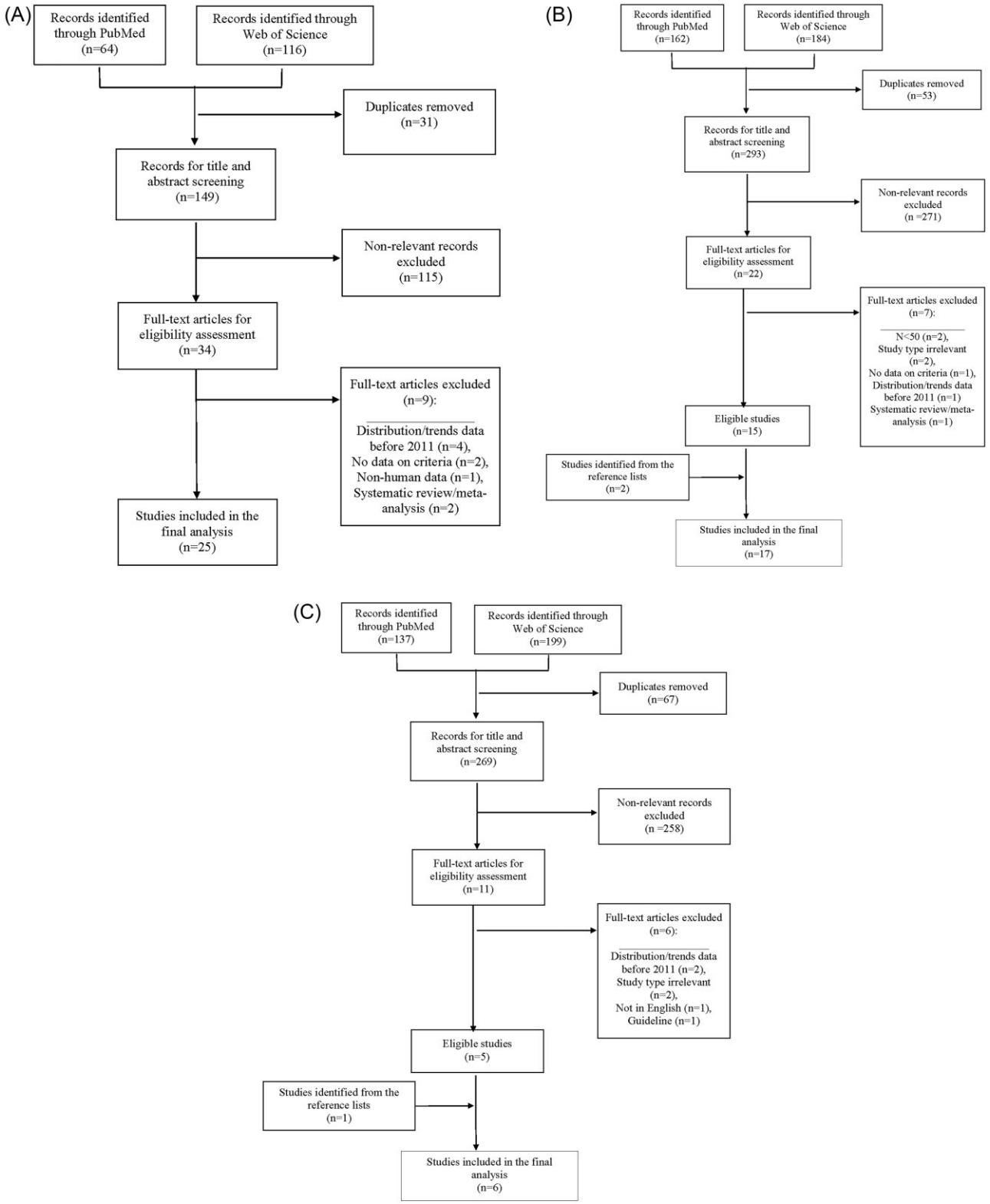

Figure 1. (a) Flow diagram for selection of studies included in the systematic review of *Talaromyces marneffei* based on: Preferred Reporting Items for Systematic review and Meta-Analyses: The PRISMA Statement. (b) Flow diagram for selection of studies included in the systematic review of *Coccidioides* species based on: Preferred Reporting Items for Systematic review and Meta-Analyses: The PRISMA Statement. (c) Flow diagram for selection of studies included in the systematic review of *Paracoccidioides* species based on: Preferred Reporting Items for Systematic review and Meta-Analyses: The PRISMA Statement.

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Table 1. Overall risk of bias for the included studies for *Talaromyces marneffei*, *Coccidioides* species, and *Paracoccidioides* species.

Author	Year	Risk	Reference
Talaromyces marneffei			
Chayakulkeeree et al.	2017	Unclear	75
Chen et al.	2017	Low	47
Dong et al.	2019	Unclear	89
Fan et al.	2017	Unclear	51
Guo et al.	2019	Unclear	52
Jiang et al.	2019	Low	48
Jiang et al.	2019	Low	10
Lao et al.	2019	Low	90
Lau et al.	2017	Unclear	62
Le et al.	2019	Low	68
Le et al.	2017	Low	49
Lei et al.	2018	Unclear	63
Li et al.	2021	Low	76
Ouyang et al.	2017	Unclear	64
Pang et al.	2018	Low	91
Qi et al.	2016	Low	92
Qiu et al.	2019	Low	93
Qiu et al.	2015	Low	94
Roohani et al.	2018	Unclear	95
Sun et al.	2021	Low	88
Sun et al.	2020	Low	96
Wang et al.	2015	Low	69
Xiao et al.	2013	Low	97
Ying et al.	2020	Low	50
Zhang et al.	2021	Unclear	65
Coccidioides species			
Benedict et al.	2019	Low	77
Blair et al.	2014	Unclear	98
Charalambous et al.	2018	Low	60
Choi et al.	2019	Low	70
Gaona-Flores et al.	2016	Low	99
Keckich et al.	2011	Unclear	84
Laws et al.	2018	Low	71
Lee et al.	2017	Unclear	54
Luo et al.	2017	Low	55
Mendoza et al.	2015	Unclear	57
Naeem et al.	2019	Low	56
Phonphok et al.	2018	Unclear	78
Sondermeyer et al.	2013	Low	61
Thompson et al.	2017	Unclear	66
Webb et al.	2018	Low	53
Wiederhold et al.	2018	Unclear	67
Wilken et al.	2015	Unclear	
Paracoccidioides species			
de Almeida et al.	2017	Unclear	58
de Macedo et al.	2017	Low	37
do Valle et al.	2017	Unclear	74
Magalhães et al.	2014	Unclear	73
Marques et al.	2013	Unclear	72
Vieira et al.	2014	High	31

Risk of bias

The overall risk of bias for each study of *T. marneffei*, *Coccidioides* spp., and *Paracoccidioides* spp. is presented in Table 1. Most (16/25 [64%]) studies examining *T. marneffei* were classified as low risk of bias in the domains used for classification (study design, data collection, or data analysis). Nine studies on *T. marneffei* (36%) were classified as unclear risk of bias, mostly due to unclear confirmation/consideration of confounding variables (8/9 [88.9%]) (Supplementary Table 1). Nine (52.9%) of the studies examining *Coccidioides* spp. were classified as low risk of bias in the domains used for classification. The remainder of the studies on *Coccidioides* spp. (47.1%) were classified as unclear risk of bias, mainly due to unclear confirmation/consideration of confounding variables (6/8 [75%]) (Supplementary Table 1). Only one (16.7%) of the included studies on *Paracoccidioides* spp. was classified as low risk of bias in the domains used for classification, and four (66.7%) were classified as unclear risk of bias; most commonly due to unclear confirmation/consideration of confounding variables (2/4 [50%]) (Supplementary Table 1).

Analysis of the criteria

Mortality

Mortality rates due to talaromycosis in adults with HIV infection ranged from 6.5% to 21%; although measured at different time points (from hospital admission, at 2 and 24 weeks from commencement of antifungal therapy) (Table 2).[47–50]In the Itraconazole versus amphotericin B for penicilliosis (IVAP), RCT performed in Vietnam of adult HIV-infected patients with talaromycosis, the 24-week mortality rate was significantly greater in the itraconazole-treated group compared with the amphotericin B deoxycholate-treated group (21% vs. 11.3%, $P = .006$), but not at 2 weeks (7.4% vs. 6.5%) (Table 2).[49]

Two studies showed high rates of mortality (36.36%–80.0%) but in small numbers of HIV-negative pediatric patients ($n = 11$ and 10, respectively) (Table 2).[51,52] Jiang et al. reported a mortality rate of 17.5% in 1093 patients who had HIV/AIDS and talaromycosis, which was 1.8–4.5-fold higher than in HIV/AIDS patients without talaromycosis (Table 2).[48]

A multicenter study from the USA reported a Day 42 and 1-year all-cause mortality of 7.4% and 12.8%, respectively, in 849 adults and children with dimorphic fungal infections. Most of which were due to *Coccidioides* spp. (93%) (Table 2).[53] Other studies in adults reported mortality rates of 2% in prisoners and 2.7% during hospital admission (Table 2).[54,55] Similarly, mortality rates were low in children (2%–3.2%), even in those with disseminated disease (3%) (Table 2).[55,56] Higher mortality rates (45%) were reported in patients who had coccidioidomycosis and were also less than 2 years post-allogeneic hematopoietic stem cell transplant (HSCT), although the patient numbers were low ($n = 11$) (Table 2).[57]

In patients with paracoccidioidomycosis, mortality rates varied widely (2.6%–32.2%) in three Brazilian studies (Table 2).[31,37,58] Mortality rates were higher (32.2%) in patients who had paracoccidioidomycosis and HIV than in those with paracoccidioidomycosis alone (20%) (Table 2).[58] de Macedo et al. reported a mortality rate of 3.4% in patients with acute juvenile paracoccidioidomycosis (average age, 23 years) (Table 2).[37]

Inpatient care, complications, and sequelae

Two single-center studies from China reported on the length of stay (LOS) in those with talaromycosis (Supplementary Table 2).[50,51] One reported a median LOS of 27 (interquartile range [IQR] 17–36) days in 1079 adult patients with HIV.[50] The second reported a LOS that ranged from 1 to 67 days in pediatric, HIV-negative patients, although this study had small numbers ($n = 10$) (Supplementary Table 2).[51]

In patients with coccidioidomycosis, hospitalization was common (20%–84%) (Supplementary Table 2).[53,56,59] In most studies (83.3%), the mean/median LOS was short (3–

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Table 2. Mortality from invasive fungal disease due to *Talaromyces marneffei, Coccidioides* species, and *Paracoccidioides* species.

Author	Year	Study design	Study period	Country	Level of care	Population description (*N*)	Number of patients (*N*)	Mortality type *n/N* (%)
Talaromyces marneffei								
Chen et al.[47]	2017	RCS SC	2014–2015	China	Tertiary	Adults with HIV and *Talaromyces marneffei* infection (81.3% disseminated)	48	NS: 8/48 (16.7%) dead at a median of 15 days (range: 7–65 days) after admission
Fan et al.[51]	2017	RCS SC	2011–2015	China	Tertiary	HIV negative children with *Talaromyces marneffei* infection	10	Overall mortality: 8/10 (80%) Range of 1–17 days post-hospitalization
Guo et al.[52]	2019	RCS SC	2013–2018	China	Tertiary	HIV negative children with disseminated talaromycosis	11	NS: 4/11 (36.36%)
Jiang et al.[48]	2019	RCS SC	2012–2105	China	Tertiary	Adults and children with HIV/AIDS and *Talaromyces marneffei* infection	1093	In-hospital mortality: 191/1093 (17.5%)
Le et al.[49]	2017	RCT MC	2012–2015	Vietnam	Tertiary	Adults with HIV infection and *Talaromyces marneffei* infection (70% with positive blood cultures)	Total: 440 Amphotericin B arm: 219 Itraconazole arm: 221	2-week mortality: 14/217 (6.5%) in the amphotericin B arm vs. 16/218 (7.4%) in the itraconazole arm Absolute risk difference: 0.9 percentage points 95% CI: −3.9 to 5.6; $P < .001$ for non-inferiority 24-week mortality: 24/219 (6.4%) in the amphotericin B arm vs. 16/221 (7.2%) in the itraconazole arm Absolute risk difference 9.7 percentage points 95% CI: 2.8–16.6; $P = .006$

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Table 2. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description (*N*)	Number of patients (*N*)	Mortality type *n*/*N* (%)
Qiu et al.[93]	2019	RCS SC	2003–2014	China	Tertiary	Adults and children with *Talaromyces marneffei* infection of the respiratory tract	Total: 63 HIV positive: 33 HIV negative: 30	No antifungal treatment: 7/7 (100%) died Antifungal treatment: 15/56 (26.7%) died
Qiu et al.[94]	2015	RCS SC	2003–2015	China	Tertiary	HIV negative adults and children with *Talaromyces marneffei* infection with or without an underlying disease*	Total: 43 With an underlying disease*: 18 Without an underlying disease*: 25	NS: At a median of 580.95 days (range: 4–2345 days): 21 (48.83%) alive Patients without an underlying disease* had significantly lower mortality: $P = .014$
Ying et al.[50]	2020	RCS SC	2011–2017	China	Tertiary	HIV-associated talaromycosis	Total: 7575 With talaromycosis: 1214 With complete data: 1079	In-hospital mortality: 86/1079 (8.0%) 90-day mortality: 128/1079 (11.9%)
Coccidioides species								
Lee et al.[54]	2017	RCS SC	2005–2006	United States	Community	Adult prison inmates with coccidioidomycosis	166	NS: 4 (2%)
Luo et al.[55]	2017	RCS MC	2005–2012	United States	Various	Adults and children hospitalized with coccidioidomycosis	Total: 30 870 Adults: 29 584 Children: 1286	Overall, in-hospital mortality: Adults: 2.7% Children: 3.2%

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Table 2. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description (*N*)	Number of patients (*N*)	Mortality type *n*/*N* (%)
Mendoza et al.[57]	2015	RCS SC	2003–2013	United States	Tertiary	Allogeneic HSCT recipients with active coccidioidomycosis	Total: 426 With coccidioidomycosis: 11 (2.6%)	Within the first 2 years post-allogeneic HSCT: 5/11 (45%)
Naeem et al.[56]	2019	RCS SC	2007–2016	United States	Tertiary	Patients ≤21 years old with extrapulmonary coccidioidomycosis	78	NS: 2% Disseminated disease: 2/63 (3%)
Webb et al.[53]	2018	RCS MC	2006–2015	United States	Various	Patients with possible, probable or proven IFI[#]	Total: 3154 patients (3374 episodes) Coccidioidomycosis: 790 (93% of 849 dimorphic fungi)	Day 42 all-cause mortality: 63 (7.4%) 1-year all-cause mortality: 109 (12.8%)
Paracoccidioides species								
de Almeida et al.[58]	2017	CCS SC	1993–2014	Brazil	Tertiary	Patients with paracoccidioidomycosis infection with or without HIV	Total: 95 With HIV: 31 Without HIV: 64	Overall mortality: With HIV: 10 (32.2%) Without HIV: 8 (20%)
de Macedo et al.[37]	2017	RCS SC	2001–2009	Brazil	Tertiary	Patients with acute juvenile paracoccidioidomycosis	29	NS: 1/29 (3.4%)[$]
Vieira et al.[31]	2014	RCS SC	1997–2012	Brazil	Tertiary	Patients with paracoccidioidomycosis	2163	NS: 131/2163 (6.05%): Range: 2.6%–22.7% during the study period Year with highest percentage: 2011 (22.7%)

N, number; *n*/*N*, number that died/number included; RCS, retrospective cohort study; SC, single center; HIV, human immunodeficiency virus; NS, not stated; AIDS, acquired immunodeficiency syndrome; MC, multicenter; CI, confidence interval; IFI, invasive fungal infection; and CCS, case control study.

[*]Underlying disease: diabetes mellitus, β-thalassemia, breast cancer, lymphoma, prior corticosteroid therapy, Langerham cell histiocytosis, G-6PD deficiency, hyperthyroidism, systemic lupus erythematosus, and chronic hepatitis B.

[#]Classified according to the European Organization for the Treatment and Research of Cancer/Mycoses Study Group criteria for the diagnosis of invasive fungal disease.[100]

[$]Neurological paracoccidioidomycosis.

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7 days) (Supplementary Table 2).[53,55,59–61] In 78 children and adolescents (≤21 years of age) with extrapulmonary coccidioidomycosis, a longer median LOS was reported (30 days [IQR 51–129] days) (Supplementary Table 2).[56] The cumulative LOS in one study of 315 patients, 1 year and 5 years after coccidioidal meningitis diagnosis, was 28.9 and 48.1 days, respectively.[60] Another study of 29 584 adults and 1286 children reported a decrease in cumulative LOS from 49 856 days in 2006 to 27 895 days in 2012 (Supplementary Table 2).[55] No data on hospital LOS stay due to paracoccidioidomycosis were reported in the studies included in this systematic review.

In the IVAP trial of adults with HIV-associated talaromycosis treated with amphotericin B or itraconazole complications included relapse of talaromycosis (1.5% vs. 7%, respectively; $P = .005$) and immune reconstitution inflammatory syndrome (0% vs. 6.6%, respectively; $P < .001$) (Table 3).[49]

A very high rate of dissemination (81%) was reported in 78 children and adolescents (≤21 years of age) with extrapulmonary coccidioidomycosis; higher than reported for adults (5%) (Table 3).[56,59] Other complications included reactivation, particularly in solid organ transplant (SOT) (5/100) and allogeneic HSCT recipients 3/11(27%) (Table 3).[57] Sondermeyer et al. examined the extent and effect of coccidioidomycosis-associated hospitalizations and found that readmission rates were high at 38%, 18% developed progressive infection, and 13% developed meningitis (Table 3).[61] Coccidioidomycosis impacts function with one study of construction workers demonstrating that 83% (34/44) missed a median of 22 days of work, 5% (2/44) missed work for >18 months and 27% (11/44) had reduced work and/or exercise capacity (Table 3).[59]

In a retrospective cohort study of 29 juveniles with acute paracoccidioidomycosis, the most commonly reported sequela was low adrenal reserve (13.8% [4/29]), followed by lymphedema (6.9% [2/29]) (Table 3).[37]

Antifungal susceptibilities

Four (16%), two (11.8%), and no studies reported on the antifungal drug susceptibility profiles of *T. marneffei*, *Coccidioides* spp., and *Paracoccidioides* spp., respectively.[62–67] The methods are summarized in Supplementary Table 3. Due to a lack of established clinical breakpoints, resistance rates are not reported herein. Susceptibility can only be estimated from the included minimum inhibitory concentration (MIC) or minimum effective concentration (MEC) values (Tables 4 and 5).

Lei et al. reported that 80.4% of 189 *T. marneffei* isolates had fluconazole MIC values of ≤4 μg/ml with a geometric mean (GM) MIC of 4.074 μg/ml (Table 4).[63] Other azoles demonstrated lower MIC values, with 96.3%, 99.5%, and 88.8% of 189 *T. marneffei* isolates having MIC values of ≤0.015 μg/ml for itraconazole, posaconazole, and voriconazole, respectively (Table 4).[63] Lau et al. reported a difference in MIC values for mycelial growth forms compared with yeast growth forms for posaconazole (MIC_{90}: 0.031 μg/ml vs. 0.002 μg/ml), whereas Zhang et al. reported similar MIC values between the two growth forms (Table 4).[62,65]

Lau et al. reported anidulafungin MIC_{90}/MEC_{90} values of 8 and 2 μg/ml for the yeast and mycelial growth forms of 57 *T. marneffei* isolates, respectively (Table 5).[62] Zhang et al. reported MEC_{90} values of 16 and 4 μg/ml for caspofungin for the yeast forms and mycelial forms of 17 *T. marneffei* isolates, respectively (Table 5).[65] One study reported that all *T. marneffei* isolates ($n = 189$) had MIC values of >8 μg/ml for micafungin (Table 5).[63] Amphotericin B MIC values were low with all *T. marneffei* ($n = 189$) yeast forms having an MIC value of ≤1 μg/ml and a GM MIC value of 0.501 μg/ml (Table 5).[63] Susceptibility data for other antifungal drugs, including flucytosine, terbinafine and olorofim, were limited (Table 5).[63–65,68] One study reported GM MIC values of 0.2825, 0.1252, and 0.0007 μg/ml for flucytosine, terbinafine, and olorofim (formerly F901318; a new antifungal agent from the orotomide class), respectively ($n = 17$ *T. marneffei* isolates) (Table 5).[65]

Fluconazole showed high MIC values in 581 *Coccidioides* isolates (MIC_{90}: 16 μg/ml; GM MIC: 7.71 μg/ml) (Table 4).[66] Of these 581 *Coccidioides* isolates, 37% and 7.9% had fluconazole MIC values ≥16 and ≥32 μg/ml, respectively.[66] In this study, MIC values were lower for the other azoles: itraconazole (MIC_{90}: 0.5 μg/ml; GM MIC: 0.245 μg/ml), posaconazole (MIC_{90}: 0.25 μg/ml; GM MIC: 0.141 μg/ml), and voriconazole (MIC_{90}: 0.25 mg/l; GM MIC: 0.107 μg/ml) (Table 4).[66] Less than 1% of the 581 *Coccidioides* isolates showed MIC values ≥2 μg/ml for itraconazole, posaconazole, and voriconazole.[66]

Susceptibility of *Coccidioides* isolates to amphotericin B (MIC_{90}: 0.5 μg/ml, GM MIC: 0.247 μg/ml) was similar to the mould-active triazoles, and only 2.8% of isolates had MIC values ≥2 μg/ml.[66] A large variability in echinocandin MIC values was observed (range ≤0.015 to >8 μg/ml) (Table 5).[66] Olorofim showed low MIC values for 59 *Coccidioides* isolates (MIC_{90}: 0.015 μg/ml, GM MIC: 0.011 μg/ml) with all isolates showing MIC values of ≤0.06 μg/ml.[67]

Risk factors

A multicenter sero-surveillance study of HIV-infected patients showed that a CD4 count of <200 cells/μl was a risk factor for developing talaromycosis (odds ratio [OR] 2.90; 95% confidence interval [CI]: 1.10–7.66; $P = .032$) (Table 6).[69] The risk increased even further when the CD4 count was <50 cells/μl (OR 24.26; 95% CI: 10.63–55.36; $P < .001$) (Table 6).[69] A diagnosis of extrapulmonary tuberculosis in the previous 3 months was noted by Jiang et al. to be a risk for developing talaromycosis (adjusted hazard ratio [aHR] 1.56; 95% CI: 1.02–2.40; $P = .04$); but also found that cotrimoxazole prophylaxis was protective (aHR 0.50; 95% CI: 0.35–0.73; $P < .001$) (Table 6 and Supplementary Table 4).[10,48]

Risk factors for coccidioidomycosis in prison inmates included being an African American (adjusted odds ratio [aOR] 1.9; $P < .05$) and age ≥41 years (aOR 1.5; $P < .05$) (Table 6).[54] Increased rates of initial hospitalization were observed in African Americans (relative risk [RR] 2.09; $P < .0001$), those with increasing age (especially ≥60 years old [RR 9.50; $P < .0001$]), men (RR: 2.48; $P < .0001$), and Hispanics (RR 1.31; $P < .0001$) (Table 6).[61]

Unscreened patients taking TNF-α inhibitors were more likely than screened patients to develop symptomatic coccidioidomycosis (35/1025 vs. 11/861; $P < .01$) (Table 6).[70] Occupational dust exposure, including from the construction of solar farms, has been associated with increased coccidioidomycosis incidence. Compared with other regions surrounding construction worksites, the incidence rate ratios were 4.4–210.6 higher (Table 6).[71]

In children and adolescents with extrapulmonary coccidioidomycosis, non-Hispanic patients were more likely to experience severe disease, require more than one drug for therapy (85% vs. 70%; $P = .04$), and have *Coccidioides* complement fixation titers ≥1:32 (89% vs. 72%; $P = .04$) compared with

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Table 3. Complications and sequelae of infections due to *Talaromyces marneffei*, *Coccidioides* species, and *Paracoccidioides* species.

Author	Year	Study design	Study period	Country	Level of care	Population description	Number of patients (*N*)	Complications and sequelae
Talaromyces marneffei								
Fan et al.[51]	2017	RCSSC	2011–2015	China	Tertiary	HIV negative children with*Talaromyces marneffei* infection	10	Hemophagocytic syndrome:8/10 (80%)ARDS:8/10 (80%)DIC:7/10 (70%)Septic shock:6/10 (60%)
Le et al.[49]	2017	RCTMC	2012–2015	Vietnam	Tertiary	Adults with HIV infection and*Talaromyces marneffei* infection(70% with positive blood cultures)	Total:440Amphotericin B arm:219Itraconazole arm:221	Relapse of talaromycosis:3/217 (1.5%) in the amphotericin B arm vs.15/218 (7.0%) in the itraconazole armAbsolute risk difference:5.4 percentage points95% CI:1.6–9.3; $P = .005$IRIS:0/217 (0%) in the amphotericin B arm vs.14/218 (6.6%) in the itraconazole armAbsolute risk difference:6.6 percentage points95% CI:3.2–9.9; $P < .001$
Coccidioides species								
Keckich et al.[84]	2011	RCSSC	1999–2009	USA	Tertiary	SOT recipients with pre-transplant coccidioidomycosis	Total:100Reactivation post-transplant:5	Coccidioidal meningitis*:1Ruptured pulmonary cavity requiring resection#:1Peritonitis#:1
Lee et al.[54]	2017	RCSSC	2005–2006	USA	Various	Adult prison inmates with coccidioidomycosis	166	Hospitalized:29/166 (17%)
Mendoza et al.[57]	2015	RCSSC	2003–2013	USA	Tertiary	Allogeneic HSCT recipients with active coccidioidomycosis	Total:426With coccidioidomycosis:11 (2.6%)	Reactivation^:3/11 (27%)Hospitalized:9/11 (82%)
Naeem et al.[56]	2019	RCSSC	2007–2016	USA	Tertiary	Patients ≤21 years old with extrapulmonary coccidioidomycosis	78	Disseminated:63/78 (81%)

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Table 3. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description	Number of patients (*N*)	Complications and sequelae
Sondermeyer et al.[61]	2013	RCSMC	2000–2011	USA	Tertiary	Coccidioidomycosis-associated hospitalizations[$]	Total over time:25 2172000: 10742011:3197	Re-admissions:9470/25 217 (38%)Re-admitted ≥3 times:1074/25 217 (4%)Progressive infection[&]:4539/25 217 (18%)Coccidioidal meningitis[&]:3208/25 217 (13%)
Wilken et al.[59]	2015	OA	2012–2014	USA	CDPH	Construction workers from two solar farms in California	Total:3572 Coccidioidomycosis:44	Disseminated:2/44 (5%)Missed work for a median 22 days:34/44 (83%)Missed work for >8 months:2/44 (5%)Experiencing health effects that interfered with work or physical activity:11/44 (27%)
Paracoccidioides species de Macedo et al.[37]	2017	RCSSC	2001–2009	Brazil	Tertiary	Patients with acute juvenile paracoccidioidomycosis	29	Impaired adrenal reserve:4/29 (13.8%)Lymphedema:2 (6.9%)Spleen calcifications:1 (3.4%)Keloids:1 (3.4%)

N, number; RCS, retrospective cohort study; SC, single center; HIV, human immunodeficiency virus; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulopathy; MC, multicenter; CI, confidence interval; IRIS, immune reconstitution inflammatory syndrome; USA, United States of America; SOT, solid organ transplant; HSCT, hematopoietic stem cell transplant; OA, outbreak analysis; and CDPH, California Department of Public Health.

[*]Occurred 1-week post-transplant and resulted in poor neurological function.

[#]Occured 3 years post-transplant in both cases.

[^]Symptomatic infection pre-transplant ($n = 1$); asymptomatic infection with positive serology pre-transplant ($n = 2$).

[$]Identified from the California Patient Discharge Data Set.

[&]Rate of hospitalization was twofold higher in 2011 compared with 2000 (1346/100 000 population vs. 276/100 000 population; $P < .0001$).

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Table 4. Susceptibility testing of *Talaromyces marneffei and Coccidioides* species to azole antifungal agents.

Author	Year	MIC determination method	Fluconazole	Itraconazole	Posaconazole	Voriconazole
Talaromyces marneffei						
Lau et al.[62]	2017	CLSI M27-A3 (for yeast forms) % MIC agreement using *E*-test CLSI M38-A2 (for mycelial forms)		MIC (μg/ml) ($n = 57$) MIC_{50}: 0.004 MIC_{90}: 0.004 Range: 0.002–0.004 100% MIC agreement using *E*-test	MIC (μg/ml) ($n = 57$) MIC_{50}: 0.002 MIC_{90}: 0.002 Range: 0.001–0.002 100% MIC agreement using *E*-test Mycelial form: MIC (μg/ml) ($n = 57$) MIC_{50}: 0.016 MIC_{90}: 0.031 Range: 0.004–0.063	MIC (μg/ml) ($n = 57$) MIC_{50}: 0.031 MIC_{90}: 0.063 Range: 0.016–0.063 31.58% MIC agreement using *E*-test
Lei et al.[63]	2018	Sensititre YeastOne™ YO10 assay Yeast forms only	MIC (μg/ml) ($n = 189$) GM: 4.074 MIC $\leq$4 (80.4% of isolates) Range: 1–32	MIC (μg/ml) ($n = 189$) GM: 0.024 MIC $\leq$0.015 (96.3% of isolates) Range: $\leq$0.015–0.03	MIC (μg/ml) ($n = 189$) GM: 0.013 MIC $\leq$0.015 (99.5% of isolates) Range: $\leq$0.015–0.06	MIC (μg/ml) ($n = 189$) GM: 0.016 MIC $\leq$0.015 (88.8% of isolates) Range: $\leq$0.015–0.06
Ouyang et al.[64]	2017	CLSI M27-A3	MIC (mg/l) ($n = 17$) Range: 0.06–4	MIC (mg/l) ($n = 17$) Range: 0.0039–0.03		MIC (mg/l) ($n = 17$) Range: 0.0078–0.015
Zhang et al.[65]	2021	CLSI M27-ED4 (for yeast forms) CLSI M38-ED3 (for mycelial forms)		MIC (μg/ml) ($n = 17$ clinical) Yeast form: GM: 0.016 MIC_{50}: 0.016 MIC_{90}: 0.016 Range: $\leq$0.016 Mycelial form: GM: 0.016 MIC_{50}: 0.016 MIC_{90}: 0.016 Range: $\leq$0.016	MIC (μg/ml) ($n = 17$ clinical) Yeast form: GM: 0.016 MIC_{50}: 0.016 MIC_{90}: 0.016 Range: $\leq$0.016 Mycelial form: GM: 0.016 MIC_{50}: 0.016 MIC_{90}: 0.016 Range: $\leq$0.016	MIC (μg/ml) ($n = 17$ clinical) Yeast form: GM: 0.0173 MIC_{50}: 0.016 MIC_{90}: 0.031 Range: $\leq$0.016–0.031 Mycelial form: GM: 0.419 MIC_{50}: 0.063 MIC_{90}: 0.063 Range: $\leq$0.016–0.063

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Table 4. Continued

Author	Year	MIC determination method	Fluconazole	Itraconazole	Posaconazole	Voriconazole
Coccidioides species Thompson et al.[66]	2017	CLSI M38-A2	MIC (μg/ml) ($n = 581$) GM: 7.710 MIC_{50}: 8 MIC_{90}: 16 Range: ≤0.12 to ≥64	MIC (μg/ml) ($n = 486$) GM: 0.245 MIC_{50}: 0.25 MIC_{90}: 0.5 Range: ≤0.03 to >16	MIC (μg/ml) ($n = 377$) GM: 0.141 MIC_{50}: 0.125 MIC_{90}: 0.25 Range: ≤0.03 to >16	MIC (μg/ml) ($n = 499$) GM: 0.107 MIC_{50}: 0.125 MIC_{90}: 0.25 Range: ≤0.015–8
Wiederhold et al.[67]	2018	CLSI M38-A2				MIC (μg/ml) All *Coccidioides* isolates ($n = 59$) GM: 0.113 MIC_{50}: 0.125 MIC_{90}: 0.25 Range: ≤0.03–0.25 *Coccidioides immitis* ($n = 21$) GM: 0.072 MIC_{50}: 0.06 MIC_{90}: 0.125 Range: ≤0.03–0.25 *Coccidioides posadasii* ($n = 24$) GM: 0.103 MIC_{50}: 0.125 MIC_{90}: 0.125 Range: ≤0.03–0.25

Data reported as it appears in the source papers.
MIC, minimum inhibitory concentration; CLSI, Clinical and Laboratory Standards Institute; MIC_{50}, MIC required to inhibit the growth of 50% of isolates; MIC_{90}, MIC required to inhibit the growth of 90% of isolates; *n*, number; and GM, geometric mean.

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Table 5. Susceptibility testing of *Talaromyces marneffei* and *Coccidioides* species to other antifungal agents.

Author	Yr	MIC method	AFG	CSG	MCG	AMB	5-FC	TER	Olorofim
Talaromyces marneffei									
Lau et al.[62]	2017	CLSI M27-A3 (for yeast forms) % MIC agreement using *E*-test CLSI M38-A2 (for mycelial forms)	MIC (μg/ml)* ($n = 57$) MIC_{50}: 4 MIC_{90}: 8 Range: 2–8 24.56% MIC agreement using *E*-test Mycelial form: MEC (μg/ml)* ($n = 57$) MIC_{50}: 1 MIC_{90}: 2 Range: 1–2						
Le et al.[68]	2019	CLSI M27-A3				MIC (mg/l) ($n = 54$) Modal: 0.5 Range: 0.25–1 Cumulative % of patients with MIC of: 0.25: 74% 0.5: 79.6% 1: 100%			
Lei et al.[63]	2018	Sensititre YeastOne™ YO10 assay Yeast forms only	MIC (μg/ml)* ($n = 189$) Range: 2 to >8 $\geq$2 for all isolates	MIC (μg/ml)* ($n = 189$) Range: 2 to >8 $\geq$2 for all isolates	MIC (μg/ml)* ($n = 189$) Range: >8 >8 all isolates	MIC (μg/ml) ($n = 189$) GM: 0.501 Range: $\leq$0.12 to 1 $\leq$1 for all isolates			
Ouyang et al.[64]	2017	CLSI M27-A3				MIC (mg/l) ($n = 17$) Range: 1–2			

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Table 5. Continued

Author	Yr	MIC method	AFG	CSG	MCG	AMB	5-FC	TER	Olorofim
Zhang et al.[65]	2021	CLSI M27-ED4 (for yeast forms) CLSI M38-ED3 (for mycelial forms)		MEC (μg/ml) ($n = 17$ clinical) Yeast form: GM: 2.6606 MEC_{50}: 2 MEC_{90}: 16 Range: 0.25–32		MIC (μg/ml) ($n = 17$ clinical) Yeast form: GM: 0.1252 MIC_{50}: 0.125 MIC_{90}: 0.5 Range: 0.03–1	MIC (μg/ml) ($n = 17$ clinical) Yeast form: GM: 0.2825 MIC_{50}: 0.25 MIC_{90}: 1 Range: 0.031–2	MIC (μg/ml) ($n = 17$ clinical) Yeast form: GM: 0.1252 MIC_{50}: 0.125 MIC_{90}: 0.25 Range: 0.031–0.5	MIC (μg/ml) ($n = 17$ clinical) Yeast form: GM: 0.0007 MIC_{50}: 0.0005 MIC_{90}: 0.002 Range: 0.00025–0.002
				Mycelial form: GM: 1.8434 MEC_{50}: 2 MEC_{90}: 4 Range: 0.5–4		Mycelial form: GM: 2 MIC_{50}: 2 MIC_{90}: 4 Range: 0.5–4	Mycelial form: GM: 0.0834 MIC_{50}: 0.063 MIC_{90}: 0.125 Range: 0.031–1	Mycelial form: GM: 0.1471 MIC_{50}: 0.125 MIC_{90}: 0.25 Range: 0.125–0.25	Mycelial form: GM: 0.0005 MIC_{50}: 0.0005 MIC_{90}: 0.0005 Range: 0.0005–0.001
Coccidioides species									
Thompson et al.[66]	2017	CLSI M38-A2	MIC (μg/ml)* ($n = 581$) GM: 0.114 MIC_{50}: 0.06 MIC_{90}: 0.25 Range: ≤0.015 to ≥8	MIC (μg/ml)* ($n = 581$) GM: 0.188 MIC_{50}: 0.125 MIC_{90}: 8 Range: ≤0.015 to ≥8	MIC (μg/ml)* ($n = 581$) GM: 0.089 MIC_{50}: 0.06 MIC_{90}: 0.125 Range: <0.015 to 8	MIC (μg/ml) ($n = 581$) GM: 0.247 MIC_{50}: 0.25 MIC_{90}: 0.5 Range: ≤0.03–4			

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Table 5. Continued

Author	Yr	MIC method	AFG	CSG	MCG	AMB	5-FC	TER	Olorofim
Wiederhold et al.[67]	2018	CLSI M38-A2							MIC (μg/ml) All *Coccidioides* isolates ($n = 59$) GM: 0.011 MIC_{50}: ≤0.008 MIC_{90}: 0.015 Range: ≤0.008–0.06 *Coccidioides immitis* ($n = 21$) GM: 0.009 MIC_{50}: ≤0.008 MIC_{90}: 0.015 Range: ≤0.008–0.015 *Coccidioides posadasii* ($n = 24$) GM: 0.009 MIC_{50}: ≤0.008 MIC_{90}: 0.015 Range: ≤0.008–0.015

Data reported as it appears in the source papers.
Yr, year; MIC, minimum inhibitory concentration; AFG, anidulafungin; CSG, caspofungin; MCG, micafungin; AMB, amphotericin B; 5-FC, 5 flucytosine; TER, terbinafine; CLSI, Clinical and Laboratory Standards Institute; *n*, number; MIC_{50}, MIC required to inhibit the growth of 50% of isolates; MIC_{90}, MIC required to inhibit the growth of 90% of isolates; MEC, minimum effective concentration; GM, geometric mean; MEC_{50}, 50% minimum effective concentration; and MEC_{90}, 90% minimum effective concentration.
*Reported as an MIC not as an MEC value.

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Table 6. Risk factors for *Talaromyces marneffei*, *Coccidioides* species, and *Paracoccidioides* species.

Author	Year	Study design	Study period	Country	Level of care	Population description	Number of patients (*N*)	Risk factor
Talaromyces marneffei								
Chen et al.[47]	2017	RCSSC	2014–2015	China	Tertiary	Adults with HIV and *Talaromyces marneffei* infection(81.3% disseminated)	48	Prognostic factors:Low CD4 count:2.5 (2–96) cells/mm^{3}vs.15 (1–163) cells/mm^3:$P < .05$Low hemoglobin:74.0 ± 19.2 g/lvs.98.5 ± 20.6 g/l:$P < .01$
Dong et al.[89]	2019	PCSSC	2016–2018	China	Tertiary	Adults with AIDS and *Talaromyces marneffei* infection(100% isolated from blood)	41	Prognostic factors:TNF-α, Il-6, Il-8, Il-1β and IP-10 levels:1.4-to164-fold higher in patients who died c/w surviving patients$P < .05$
Jiang et al.[48]	2019	RCSSC	2012–2105	China	Tertiary	Adults and children with HIV/AIDS and*Talaromyces marneffei* infection	1093	Low baseline CD4 count:<50 cells/μl:aHR 5.83 (95% CI: 3.04–11.18; $P <$ .001)and50-99 cells/μl:aHR 3.43 (95% CI: 1.67–7.03; $P =$ .001)Diagnosed with extrapulmonary tuberculosis in the prior 3 months:aHR 1.56 (95% CI: 1.02–2.40; $P = .04$)
Sun et al.[88]	2021	RCSSC	2015–2020	China	Tertiary	Adults with HIV and *Talaromyces marneffei* bloodstream infection	87	Prognostic factors:Low CD8 count:<200/μl vs. >200/μl:12.6-fold higher risk($P = .04$)Low BDG:< 100 pg/ml vs. BDG > 100 pg/ml:34.9-fold higher risk($P =$ .01)
Wang et al.[69]	2015	RLSMC	2004–2011	China	Various	HIV patients with archived serum samples*	Total:8131 samples from 7734 patientsPositive for disseminated talaromycosis^:761 samples	Low CD4 count:<200 cells/μl:OR 2.90 (95% CI: 1.10–7.66; $P = .032$)and<50 cells/μl:OR 24.26 (95% CI: 10.63–55.36; $P < .001$)
Coccidioides species								
Blair et al.[98]	2014	PCSMC	2012–2013	USA	University	Employees from 2 campuses#	TOTAL:316Campus A:176Campus B:140	Regularly taking walks outdoors:adjusted OR 3.39 (95% CI: 0.74–15.49);$P =$ .11At 1 year of follow-up:3/120 (2.5%) from Campus A vs. 8/90 (8.9%) from Campus B developed CM;$P = .04$

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Table 6. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description	Number of patients (*N*)	Risk factor
Choi et al.[70]	2019	RCSSC	2010–2016	USA	Tertiary	Adults and children taking a TNF-α inhibitor	Total;1951Screened: 925/1951 (47.4%)Not screened:1025/1951 (52.5%)	Unscreened were more likely to develop symptomatic CM than screened patients:35/1025 vs. 11/861:$P < .01$
Keckich et al.[84]	2011	RCSSC	1999–2009	USA	Tertiary	SOT recipients with pre-transplant CM	Total:100Reactivation post-transplant:5	Post-transplantation risk of reactivation:Pre-transplant extrapulmonary CM:$P = .07$African American:2/5 (40%)vs.4/89 (4%):$P = .03$
Laws et al.[71]	2018	PCSSC	2016–2017	USA	Community	Workers at a solar power farm, Monterey County, California	Total:2410Workerswith CM:9	Occupational exposure:Work-site incidence rate:1095/100 000 populationvs.Other counties surrounding the solar farm:5.2–251.7/100 000PopulationRR:4.4–210.6
Lee et al.[54]	2017	RCSSC	2005–2006	USA	Community	Adult prison inmates with CM	166	Black race/ethnicity:aOR 1.9 ($P < .05$)Age ≥41 years:aOR 1.5 ($P < .05$)Residence of Yard C[&]:aOR 2.6 ($P < .05$)
Naeem et al.[56]	2019	RCSSC	2007–2016	USA	Tertiary	Patients ≤21 years old with extrapulmonary CM	78	Non-Hispanics and patients ≥10 years of age are more likely to experience severe diseaseNon-Hispanics vs. Hispanics:Required >1 drug therapy:85% vs. 70% ($P = .04$), *Coccidioides* complement fixation titers ≥1:3289% vs. 72% ($P = .04$)Children ≥0 years old vs. <10 years:>1 site of involvement 47% vs. 25% ($P = .06$), Relapsed/progressive/fatal disease21% vs. 5% ($P = .06$)
Sondermeyer et al.[61]	2013	RCSMC	2000–2011	USA	Tertiary	CM-associated hospitalizations[$]	Total over time:25 2172000:107420 11:3197	Initial hospitalization:Men:RR 2.48($P < .0001$)Increasing age:20–39 years: RR 4.22;40–59 years: RR 7.73; ≥60 years: RR 9.50($P < .0001$)African American:RR 2.09($P < .0001$)HispanicRR 1.31($P < .0001$)

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Table 6. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description	Number of patients (*N*)	Risk factor
Wilken et al.[59]	2015	OA	2012–2014	USA	CDPH	Construction workers from two solar farms in California	Total:3572CM:44	Occupational exposure during soil-disrupting activities:39/42 (93%) with coccidioidomycosiswere exposed to high dust levels at least weekly
Paracoccidioides species								
do Valle et al.[74]	2017	OASC	2008–2014(Pre)vs.2015–2016(Post)	Brazil	Tertiary	Patients with PCM	NS	Construction:1988–2015 average annual attending Evandro Chagas NIID:2.3 cases/yearFrom Baixada Fluminense:1.4 cases/year2016:From Baixada Fluminense:8 cases/yearx 5.7 increase
Magalhães et al.[73]	2014	CSS	2009	Brazil	Rural area of Alfenas-MG	People who lived in Alfenas-MG	Total:542Positive skin test:46.67%	Male genderOR 2.16 (95% CI: 1.53–3.05; $P < .0001$
Marques et al.[72]	2013	SPS	NS	Brazil	Rural areas of Jaraguari County	People who lived in Jaraguari County	Total:727Positive skin test45.8% (95% CI: 42.1–49.5)	Age:Higher prevalence in >40 years oldvs.≤40 years old:(adjusted PR 1.71 (95% CI: 1.33–2.21)
Vieria et al.[31]	2014	RCSMC	1997–2012	Brazil	Tertiary	Patients with PCM	2163	Male gender:90.2%Most common age:40–59 years:58.2%

N, number; RCS, retrospective cohort study; SC, single center; HIV, human immunodeficiency virus; PCS, prospective cohort study; AIDS, acquired immunodeficiency virus; TNF-α, tumor necrosis factor-alpha; IL, interleukin; IP-10, interferon-gamma inducible protein; c/w, compared with; aHR, adjusted hazard ratio; CI, confidence interval; BDG, 1,3-β-D-glucan; RLS, retrospective laboratory study; MC, multicenter; OR, odds ratio; USA, United States of America; CM, coccidioidomycosis; SOT, solid organ transplant; RR, relative ratio; aOR, adjusted odds ratio; OA, outbreak analysis; CDPH, California Department of Public Health; PCM, paracoccidioidomycosis; NS, not stated; NIID, National Institute Infectious Diseases; CSS, cross sectional survey; SPS, sero-prevalence survey; and PR, prevalence ratio.

*Archived at Centre for Disease Control and Prevention (GZCDC).

^Using the double-antibody sandwich ELISA for Mp1p antigen.

#Campus A near a construction site and campus B 13 miles away, Arizona State University, Maricopa County, Arizona, USA.

&Contained inmates with special needs (e.g., diabetes mellitus, chronic respiratory disease).

$Identified from the California Patient Discharge Data Set.

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their Hispanic counterparts.[56] Children ≥10 years old were more likely to have more than one site of involvement (47% vs. 25%; $P = .06$) and higher rate of relapse, disease progression, and/or fatal disease (21% vs. 5%; $P = .06$) compared with those <10 years of age.[56]

A higher prevalence of paracoccidioidomycosis was observed in patients >40 years old compared with patients ≤40 years old (adjusted prevalence ratio 1.71; 95% CI: 1.33–2.21) (Table 6).[72] Magalhães et al. reported that being of male gender was a risk factor for paracoccidioidomycosis (OR 2.16; 95% CI: 1.53–3.05; $P < .0001$) (Table 6).[73] In a single-center study by do Valle et al., an increase in paracoccidioidomycosis cases was observed during highway construction, resulting in 5.7 times increase in the incidence rate from 1.4 to 8 cases/year (Table 6).[74]

Annual incidence

The annual incidence of talaromycosis in Thailand was estimated at 0.3/100 000 in 2013 (Supplementary Table 5).[75] Two other single-center studies conducted in China reported incidence rates of 15.14/1000 person-year in HIV/AIDS patients and 0.17/1000–1.97/1000 patients during the years of 2013–2019 (Supplementary Table 5).[10,76] The incidence was lower in HIV-infected patients on co-trimoxazole as compared with those not on it (12.63 vs. 29.59/1000 person-year; $P < .001$) (Supplementary Table 5).[48]

In the USA, the annual incidence rates of coccidioidomycosis were variable depending on the state and were generally higher in the south-west. In Arizona and California, incidence rates between 2011 and 2017 were 85.8–260.5/100 000 and 6.0–18.2/100 000 populations, respectively (Supplementary Table 5).[77] The rates were higher in sites constructing solar farms compared with the surrounding counties (1095/100 000 vs. 5.2–251.7/100 000 persons) (Supplementary Table 5).[71]

An average annual incidence of paracoccidioidomycosis cases in the State of Rondônia in the north-west part of Brazil was 94/100 000 people during the study period of 1997–2012, but was highly variable between the state's municipalities, ranging from 16 to 391/1000 000 (Supplementary Table 5).[31] The reported incidence rates for Rio de Janeiro (south-east area of Brazil) were variable and affected by a paracoccidioidomycosis outbreak during the construction of a highway. The annual incidence of acute paracoccidioidomycosis was 1.29/1 million persons (95% CI: 0.74–4.03) before the highway construction years (before 2008) and 8.25/1 million persons (95% CI: 4.18–16.3) during the outbreak after the highway construction (2015–2016) (Supplementary Table 5).[74]

Prevalence, global distribution, and trends

Talaromycosis was frequently reported in China ($n = 12$ studies) (Supplementary Table 6). It is most prevalent in southern China (9%–16.1% of HIV-infected patients) (Supplementary Table 6).[48,50,69] In Thailand, also being an endemic area for talaromycosis, the northern part of the country was reported to have the highest prevalence (0.3/100 000 per year) especially in HIV/AIDS patients (2.6% of all new AIDS cases) (Supplementary Table 6).[75]

Coccidioidomycosis was highly distributed in certain parts of the USA, especially the south-western region. Greater than 95% of coccidioidomycosis cases were reported from Arizona and California (Supplementary Table 6).[77] In particular, the southern California Central Valley area (Kern, Kings, Tulare, and Fresno counties) and San Luis Obispo County were considered highly endemic or as having established endemicity (Supplementary Table 6).[78]

Using positive skin tests, the prevalence of paracoccidioidomycosis in the rural areas of the central-west and south-east parts of Brazil was reported as 45.8%–46.67% (Supplementary Table 6).[73] Vieira et al. reported a prevalence of 53.6% ($n = 1161$) and 46.4% ($n = 1002$) in the urban and rural areas, respectively, of the State of Rondônia (north-west area of Brazil).[31]

In the last 10 years, an increasing trend in talaromycosis cases was reported from China. Li et al. observed a 16% ($P < .001$) year-on-year increase in talaromycosis incidence between 2013 and 2019.[76] Wang et al. noted that the increasing trend of talaromycosis prevalence up until 2011 was strongly associated with progression of HIV infection to AIDS (OR 4.66; 95% CI: 3.94–5.51; $P < .001$).[69]

Trends for coccidioidomycosis in the last 10 years were assessed based on two studies from the USA.[53,77] A population-based surveillance study reported that the number of coccidioidomycosis cases decreased from 2011 to 2014 (from 22 634 to 8232), followed by an increase from 2014 to 2017 (from 8232 to 14 364), although variability was observed between states (Supplementary Table 7).[77]

In the State of Rondônia, Brazil, 44 paracoccidioidomycosis cases were reported in 2011 and 38 cases in 2012. Based on population numbers for these years, this represented approximately an 11% decrease in paracoccidioidomycosis incidence from 2.7/100 000 to 2.4/100 000; but contemporary data are lacking.[31] Data on trends in other countries or regions are also lacking.

Discussion

This systematic review examined the epidemiology, impact, and outcomes of fungal infection due to *T. marneffei*, *Coccidioides* spp., and *Paracoccidioide*s spp. Due to the predetermined inclusion/exclusion criteria, only a small number of studies were included, and many (36%–66.7%) were associated with an unclear risk of bias. Despite this, we found that mortality rates were substantial, inpatient stays and complications were common, classical endemic areas were changing, and many of these fungi were increasing in incidence.

Mortality rates due to talaromycosis in HIV-infected patients ranged from 6.5% to 21%.[47–50] However, these were measured at different time points, making it difficult to compare between studies. The 2- and 24-week mortality rates were used in the IVAP RCT to determine the comparative efficacy of itraconazole and amphotericin B deoxycholate in the treatment of HIV-associated talaromycosis.[49] Treatment of talaromycosis usually consists of induction therapy for 2 weeks, followed by consolidation therapy for 10 weeks, and then chronic maintenance therapy/secondary prophylaxis until CD4 count are >100 cell/mm^3 for ≥6 months in a patient with HIV.[49,79] As 2-week mortality rates coincide with the time point at which induction therapy ends and step-down consolidation therapy begins, this was used as the primary endpoint in the IVAP trial. However, mortality continued to rise over the 24 weeks of follow-up in both treatment groups, indicating that the 24-week follow-up window allows adequate time for the detection of significant long-term or downstream effects of therapy (e.g., relapse, immune reconstitution inflammatory syndrome, hospital readmission, treatment-emergent adverse events). Given this, we recommend that the

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24-week time point is used in addition to the 2-week time point in future studies of the treatment of talaromycosis to allow for the comparison of antifungal agents, studies, groups, and regions and determine trends over time. Other studies not eligible for inclusion in this systematic review reported higher mortality rates: 20.7%–33% in HIV-infected patients and 29.4% in HIV-negative patients likely reflecting the challenges of diagnosis and consequences of diagnostic delay.[1,80,81] Small studies of HIV-negative pediatric patients showed very high mortality rates, which may be due to non-specific presentations resulting in delayed or missed diagnosis, as reported in one study (9/11 [82%]).[48,51,52] While this needs to be confirmed in larger studies, it indicates that education and clinical practice guidelines are needed to increase awareness and the early diagnosis of talaromycosis.

Mortality rates in patients with coccidioidomycosis were low (2%–12.8%) except for immunosuppressed patients.[53–56] Patients who developed coccidioidomycosis within 2 years of allogeneic HSCT had a mortality rate of 45%.[57] Allogeneic HSCT recipients still have appreciable levels of immunodeficiency 2 years on, which may have contributed to the reported high mortality rates.[82,83] Antifungal prophylaxis may be needed in allogeneic HSCT recipients from endemic areas, especially if there is a previous history of coccidioidomycosis.[57,78,84] Mendoza et al. showed that 9/11 (82%) of those who developed coccidioidomycosis were not on antifungal prophylaxis (Supplementary Table 4).[57] The clinical implications of these data are that screening of patients prior to transplant (both allogeneic HSCT and SOT) or receiving immunosuppressive drugs (e.g., TNF-α inhibitors) should be performed and antifungal prophylaxis considered (Supplementary Table 4).[57,70,78,84] Similarly, with paracoccidioidomycosis, mortality rates were higher in those with an underlying immunosuppressive state compared with those without (32.2% HIV-infected vs. 20% HIV-negative).[58]

Hospitalization with coccidioidomycosis was common (up to 84% of cases).[53,56,59] In most studies, hospitalizations were short (mean/median LOS 3–7 days).[53,55,59–61] Cumulative LOS was noted to be high 1 and 5 years (28.9 and 48.1 days, respectively) after a diagnosis of coccidioidal meningitis.[60] Sondermeyer et al. reported a readmission rate of 38%.[61] This reflects a chronic disease that slowly improves over time and requires long durations of treatment. Coccidioidomycosis severely impacts function and quality of life with 83% of affected construction workers missing a median of 22 days of work and 27% having reduced work and/or exercise capacity.[59] Given the association of outbreaks of coccidioidomycosis with construction work, preventative measures such as workplace dust control, respiratory protection, high-efficiency particulate absorbing filtration in trucks, and detailed reporting and tracking of infections have been developed.[59,71] These measures should be implemented at the start of any construction in endemic areas.

Most patients with paracoccidioidomycosis report current or past contact with rural environments related to either their profession and/or residence. do Valle et al. reported an increase in paracoccidioidomycosis cases associated with highway construction.[74] Vieira et al. reported a mortality rate that varied widely (2.6%–22.7%) over the time of construction, with the highest rates occurring at the time of that the paracoccidioidomycosis public health program restricted treatment availability.[31] This further emphasizes the importance of preventative measures for these fungi. Paracoccidioidomycosis may be complicated by a chronic inflammatory process that results in fibrosis in organs and impairment of function.[27,34,38–40]

No studies on the antifungal susceptibility of *Paracoccidioides* spp. were identified as part of this systematic review. Most of the studies examining *Paracoccidioides* spp. antifungal susceptibility come from before 2011 and indicate that they are sensitive to most of the commonly used antifungal agents (amphotericin B, fluconazole, itraconazole, voriconazole, posaconazole, and terbinafine) and also to sulfonamides.[85] More recently, *Paracoccidioides* spp. have also been shown to be susceptible to the newer azole, isavuconazole.[86] There are no established breakpoints for *T. marneffei*, *Coccidioides* spp., and *Paracoccidioides* spp. Thus, it is currently not possible to define antifungal resistance rates or trends over time. The fluconazole MIC values were higher than the other triazoles for *T. marneffei*. Similarly, fluconazole showed higher MIC values for *Coccidioides* spp. as compared with the other triazoles.[66] Of note, *Coccidioides* spp. had very low MIC values to the new antifungal agent olorofim with all isolates showing MIC values of $\leq$0.06 μg/ml.[67] Olorofim is the first antifungal in a new class of antifungal agents that inhibit dihydroorotate dehydrogenase and consequently, pyrimidine synthesis. It has been shown to have superior *in vitro* and *in vivo* activity against *Coccidioides* spp. compared with fluconazole and may prove to be a highly effective agent in the treatment of coccidioidomycosis.[67,87]

Risk factors for developing talaromycosis include a low CD4 count, with decreasing CD4 counts associated with an increasing risk.[69] The administration of co-trimoxazole as prophylaxis was reported to decrease the risk of developing talaromycosis. This is more likely to be a confounder or surrogate for comprehensive and early HIV care, but it indicates the clinical importance of screening for HIV infection in high-risk areas and managing all aspects, including prophylaxis. African American prison inmates are at increased risk of developing coccidioidomycosis as compared with other inmates.[54] Again, this may be a surrogate marker for the disproportionate numbers and time spent in prison. However, it provides good data for developing targeted preventative strategies.

Talaromycosis was frequently reported in China and was most prevalent in the south of the country.[48,50,69] A few studies reported increasing rates over the years that correlated with HIV infection[50,88] providing further evidence for the need to develop effective strategies for the early identification and management of cases of HIV infection. A population-based study in the USA identified that coccidioidomycosis cases increased between 2014 and 2017 from 8.232 to 14 364/year.[77] However, more contemporary data are required to determine current trends. Cases of paracoccidioidomycosis decreased by 11% between 2011 and 2012 in Rondônia State, Brazil.[31] No current data are available, and data from other regions or other countries were not identified as part of this systematic review. This underscores the need for robust surveillance to accurately determine trends over time.

This systematic review has several limitations. The inclusion/exclusion criteria may have resulted in several important studies being excluded. This may have affected the findings of this systematic review. The failure to include studies in languages other than English, conference abstracts, and pre-prints may have biased the findings. This is likely very relevant for *T. marneffei*, *Coccidioides* spp., and *Paracoccidioides* spp. given they occur more commonly in non-English-

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speaking countries. The heterogeneity of the studies and the paucity of the included data limit our ability to draw any firm conclusions regarding the epidemiology, impact, and outcome of infections due to *T. marneffei*, *Coccidioides* spp., and *Paracoccidioides* spp.

Talaromyces marneffei, Coccidioides spp., and *Paracoccidioides* spp. are associated with significant morbidity and mortality. Thus, screening and prophylaxis to prevent reactivation are critical. Morbidity can be significant in those with coccidioidal meningitis and in those who develop fibrosis related to paracoccidioidomycosis, impacting ability to work. While some public health interventions have been implemented, evaluation of their efficacy is required. Clinical breakpoints need to be determined for these fungi so clinicians can develop effective treatment strategies. This requires the efforts of mycologists, globally. Future research in this area should include the performance of more comprehensive systematic reviews of *T. marneffei*, *Coccidioides* spp., and *Paracoccidioides* spp. removing the language and study period restrictions. In this setting, it is likely that formal meta-analyses (using generalized linear mixed models) could be performed. Narrative reviews, systematic reviews, meta-analyses, or network analyses should also be performed on the treatment of these pathogens. Such comprehensive reviews will result in more robust data. This, in turn, will allow for the improved identification of priorities for public health interventions and research and development for *T. marneffei*, *Coccidioides* spp., and *Paracoccidioides* spp. at a regional and local level. Most importantly, global surveillance studies are required to better determine the burden, annual incidence, global distribution, and trends of these important fungi.

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Supplementary material

Supplementary material is available at *Medical Mycology* online.

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Declaration of interest

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