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Original Article

Fusarium species,*Scedosporium* species, and *Lomentospora prolificans*: A systematic review to inform the World Health Organization priority list of fungal pathogens

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Abstract

Recognizing the growing global burden of fungal infections, the World Health Organization established a process to develop a priority list of fungal pathogens (FPPL). In this systematic review, we aimed to evaluate the epidemiology and impact of infections caused by *Fusarium* spp., *Scedosporium* spp., and *Lomentospora prolificans* to inform the first FPPL. PubMed and Web of Sciences databases were searched to identify studies published between January 1, 2011 and February 23, 2021, reporting on mortality, complications and sequelae, antifungal susceptibility, preventability, annual incidence, and trends. Overall, 20, 11, and 9 articles were included for *Fusarium* spp., *Scedosporium* spp., and *L. prolificans*, respectively. Mortality rates were high in those with invasive fusariosis, scedosporiosis, and lomentosporiosis (42.9%–66.7%, 42.4%–46.9%, and 50.0%–71.4%, respectively). Antifungal susceptibility data, based on small isolate numbers, showed high minimum inhibitory concentrations (MIC)/minimum effective concentrations for most currently available antifungal agents. The median/mode MIC for itraconazole and isavuconazole were ≥16 mg/l for all three pathogens. Based on limited data, these fungi are emerging. Invasive fusariosis increased from 0.08 cases/100 000 admissions to 0.22 cases/100 000 admissions over the time periods of 2000–2009 and 2010–2015, respectively, and in lung transplant recipients, *Scedosporium* spp. and *L. prolificans* were only detected from 2014 onwards. Global surveillance to better delineate antifungal susceptibility, risk factors, sequelae, and outcomes is required.

Key words: *Fusarium, Scedosporium apiospermum, Lomentospora prolificans,* invasive fungal disease, fungemia, antifungal resistance, mortality, epidemiology.

Introduction

Fusarium species (spp.), *Scedosporium* species (spp.), and *Lomentospora prolificans* are mycelial moulds classified as hyphomycetes. While phylogenetically and morphologically distinct, these pathogens have several similarities including their propensity to cause localized infections in immunocompetent hosts and disseminated infections in immunocompromised hosts. These fungi are difficult to treat, owing to intrinsic multidrug resistance, and are reported to be on the increase.[1,2]

Fusarium spp. are ubiquitous in the environment and cause disease in plants, animals, and humans. The distribution of human disease is worldwide, and *Fusarium* has been reported as a hospital-acquired pathogen.[3] While more than 70 species can cause fusariosis, *F. solani* species complex (SC) and *F. oxysporum* SC are responsible for 50%–60% and 20% of human cases, respectively.[4–6] *Fusarium* spp. typically enter the host through the airways or direct mucocutaneous inoculation, resulting in superficial (keratitis and onychomycosis), locally invasive (cellulitis, sinusitis), or disseminated infections (often with positive blood cultures).[7] Dissemination is facilitated by adventitial sporulation and classically occurs in immunocompromised patients, especially those who are neutropenic or have impaired T-cell immunity. Prognosis is dependent on the immune status of the host, with poor survival seen in those with hematologic malignancies.[8]

Scedosporium spp. and *L. prolificans* are pathogenic fungi that survive in various environments, including sewage and decaying matter.[9–11] The genus *Scedosporium* contains at least 10 species of which *S. apiospermum* and *S. boydii* are the most frequently isolated and distributed worldwide. *Scedosporium aurantiacum* is more common in parts of Europe and Australia, accounting for 50% of all environmental *Scedosporium* isolates.[11,12] *Lomentospora prolificans* (formerly *S. prolificans*) is morphologically and phylogenetically distinct from *Scedosporium* spp. and occurs mainly in Australia, Spain, and the United States of America.[12,13] In immunocompromised hosts, *Scedosporium* spp. and *L. prolificans* most commonly cause invasive fungal disease (IFD). Angioinvasion and adventitial sporulation in tissue facilitate dissemination, and blood cultures are frequently positive.[14,15] Dissemination is more common in hematopoietic stem cell transplant (HSCT) recipients compared with solid organ transplant recipients (SOT), and the attributable mortality in those with acute leukemia is up to 77%.[16,17] In immunocompetent hosts, *Scedosporium* spp. can cause localized infection of the skin, muscles, bones, and joints, particularly following trauma and brain abscesses following near-drowning. Pulmonary colonization with *Scedosporium* spp. and *L. prolificans* is typically associated with structural lung disease, such as bronchiectasis and cystic fibrosis (CF), resulting in chronic inflammation and the potential for progression to IFD in those who go on to lung transplantation or develop a hematologic malignancy.[12,18–20]

Given their increasing importance, this systematic review aimed to evaluate infections due to *Fusarium* spp., *Scedosporium* spp., and *L. prolificans* 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 January 1, 2011 to February 23, 2021. The generated data identified knowledge gaps for *Fusarium* spp., *Scedosporium* spp., and *L. prolificans* informing the fungal priority pathogens list (FFPL) of the World Health Organization (WHO).[21]

Methods

Study design

A systematic review was performed using the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Guidelines.[22]

Inclusion and exclusion criteria

Studies were included if they reported data on the following: (a) adults and/or pediatric populations; (b) *Fusarium* spp., *Scedosporium* spp., or *L. prolificans*; (c) at least 1 criterion (mortality, inpatient care [hospital length of stay], complications/sequelae, antifungal susceptibility, preventability [preventive measures]), annual incidence, global distribution, and emergence [increasing in incidence or geographical range]) in the prior 10 years; (d) retrospective or prospective observational studies, randomized controlled trials, epidemiological or surveillance studies; and (e) were published between January 1, 2011 and February 23, 2021. Studies were excluded if they had/were: (a) non-human data only (animals and plants only); (b) non-fungal data only (bacteria, viruses, and parasites only); (c) no data on the relevant pathogens or criteria; (d) data on novel antifungals in pre-clinical studies or early-phase trials or non-licensed antifungals only; (e) data on *in*

vitro resistance mechanisms only; (f) case reports or conference abstracts; (g) not in English; and (h) 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 January 1, 2011 and February 23, 2021. On PubMed, the search was optimized using medical subject headings (MeSH) and/or keyword terms in the title/abstract for *Fusarium* spp., *Scedosporium* spp., or *L. prolificans* and each criterion. On the Web of Science, MeSH terms are not available, and therefore topic search (TS), title (TI), or abstract (AB) search was used. The final searches are detailed in the supplementary materials.

PubMed and related databases are underpinned by a standardized taxonomy database. Thus, using a species name as a search term retrieved articles containing obsolete or updated nomenclature.[23]

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 inclusion criteria, and no reasons were provided for excluding articles at this step. Then, full text screening was performed on the remaining articles to determine eligibility for inclusion, and the reasons for excluding any articles were recorded. The title/abstract screening and full text screenings were performed independently by (H.Y.K. and O.B.I. [*Fusarium* spp.], H.Y.K. and A.M. [*Scedosporium* spp.], H.Y.K. and J.B. [*L. prolificans*]) in Covidence®. Discrepancies were resolved by a third reviewer (J.W.A.). Any additional relevant articles identified from the reference lists of the included articles were added.

Data extraction

Data from the final set of eligible articles were extracted for each relevant criterion by the screening reviewers (H.Y.K. and J.B.) and were independently checked for accuracy by another reviewer (C.O.M.).

Risk of bias assessment

Risk of bias assessments were independently performed by two reviewers (H.Y.K. and C.O.M.) for the included studies. Risk of bias tools for randomized trials (ROB version 2) and non-randomized studies (RoBANS) were used for this assessment.[24,25] For the overall risk, using the ROB 2 tool, the studies were rated low, high, or some concerns. Using the RoBANS tool, the studies were rated as low, high, or unclear risk.

This systematic review was intended to inform on 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 (e.g., proportions [%], mean, median, range) analyzed or reported in the tables as text, depending on the amount and nature of the data.

Results

Study selection

Between January 1, 2011 and February 23, 2021, the PubMed and Web of Science Core Collection databases yielded 315 and 306 articles on *Fusarium* spp. (Fig. 1a), 210 and 251 articles on *Scedosporium* spp. (Fig. 1b), and 94 and 92 articles on *L. prolificans*, respectively (Fig. 1c). After excluding the duplicated and irrelevant articles, 40, 41, and 16 articles underwent full-text screening of which 20, 11, and 9 articles on *Fusarium* spp., *Scedosporium* spp., and *L. prolificans*, respectively, were deemed eligible for inclusion in the final analysis (Fig. 1a–c).

Risk of bias

The overall risk of bias for each study of *Fusarium* spp., *Scedosporium* spp., and *L. prolificans* is presented in Table 1. Five (25%) studies examining *Fusarium* spp. were classified as low risk of bias in the domains used for classification (i.e., study design, data collection, or data analysis). Fourteen (70%) studies on *Fusarium* spp. were classified as unclear risk of bias. This was because these studies did not define the eligibility criteria or population groups and/or consider the confounding variables (Supplementary Table 1). One (5%) study on *Fusarium* spp. was classified as high risk, as isolates were randomly selected for molecular confirmation rather than specifically selected based on the clinical meta-data.[26] For *Scedosporium* spp., seven (63.6%) studies were classified as low risk of bias in the domains used for classification. Four (36.4%) studies on *Scedosporium* spp. were classified as unclear risk of bias related to unclear eligibility criteria or population groups and/or unclear confirmation/consideration of confounding variables (Supplementary Table 1). Four (44.4%) studies of *L. prolificans* were classified as low risk of bias in the domains used for classification, and three (33.3%) were classified as unclear risk of bias, all related to unclear eligibility criteria or population groups and/or unclear confirmation/consideration of confounding variables (Supplementary Table 1). Two studies (22.2%) by Seidel et al. were classified as high risk, as the studies included data from a mixed fungal registry and from the literature.[27,28]

Analysis of the criteria

Mortality

Thirty-day mortality rates associated with invasive fusariosis ranged from 42.9% to 66.7% in three studies (Table 2).[5,29,30] High rates were seen in cases where *F. solani* SC and *F. proliferatum* were isolated (66.7% and 62.5%, respectively).[5] Perez-Nadales et al. demonstrated that 90-day mortality was significantly higher in neutropenic patients compared with non-neutropenic patients (38/58 [65.9%] vs. 17/58 [28.6%]; $P = .01$) (Table 2).[1] Four studies reported on mortality rates

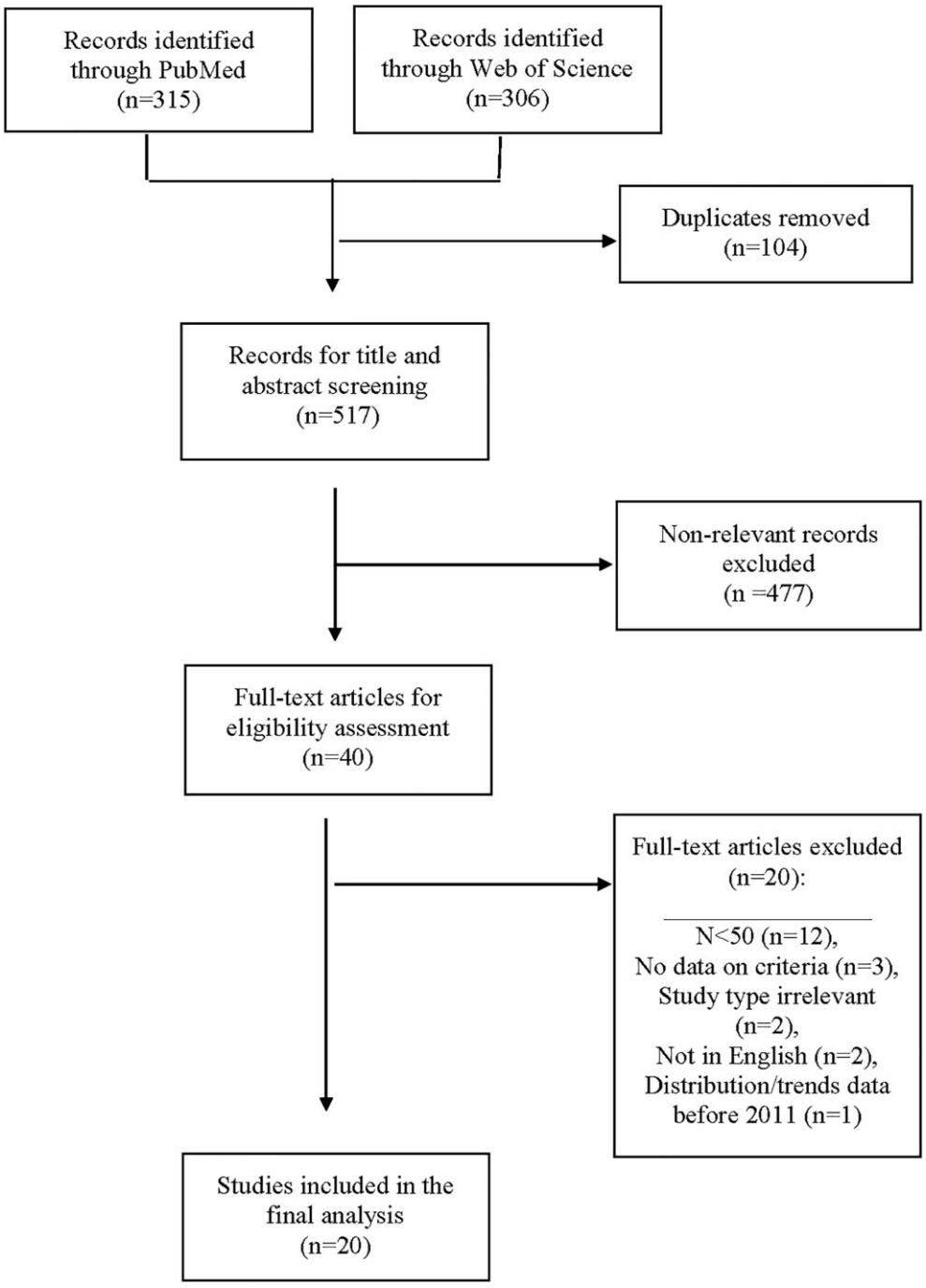

Figure 1a. Flow diagram for selection of studies included in the systematic review of *Fusarium* species. Based on: Preferred Reporting Items for Systematic Review and Meta-Analyses: The PRISMA Statement.

associated with IFD due to *Scedosporium* spp. (Table 2). Day 42 mortality was 18.2% (6/33) in an analysis of cases from the FungiScope® registry (Table 2).[27] One study found a 90-day mortality rate of 46.3% (25/54), but this study did not differentiate between IFD due to *Scedosporium* spp. or *L. prolificans*.[31] More recently, a French study reported a 90-day mortality rate of 18.6% (13/70) for invasive scedosporiosis (Table 2).[32] IFD due to *L. prolificans* is associated with significantly higher mortality rates (11/22 [50%]) compared with scedosporiosis (6/33 [18.2%]) ($P = .018$),[27] which may explain the differences observed in the 90-day mortality rates between the studies of Slavin et al. and Bronnimann et al. (Table 2).[31,32]

Inpatient care, complications, and sequelae

We found no data on the length of hospital stay for infections due to *Fusarium* spp., *Scedosporium* spp. or *L. prolificans*. Four studies reported on the complications and sequelae of keratitis and corneal ulcers due to *Fusarium* spp. (Table 3). Corneal perforations were reported in up to 30.8% of patients with *Fusarium* keratitis.[33,34] Surgical management with therapeutic penetrating keratoplasty was required in up to

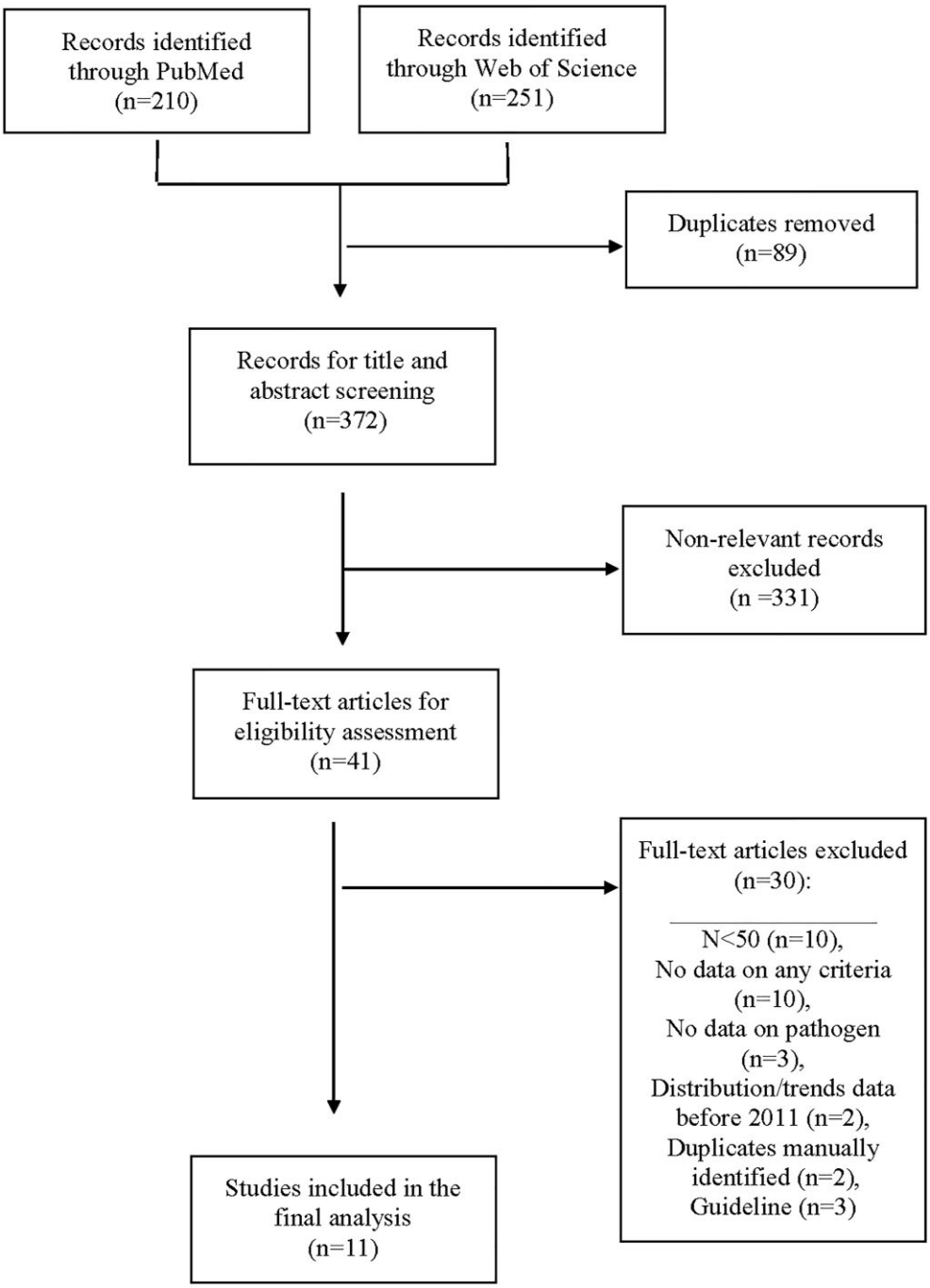

Figure 1b. Flow diagram for selection of studies included in the systematic review of *Scedosporium* species. Based on: Preferred Reporting Items for Systematic Review and Meta-Analyses: The PRISMA Statement.

83.3%,[33–35] enucleation/evisceration was performed in 7/89 (7.8%), and 20 (22.5%) had a corneal transplant[36] (Table 3). No study reported on the complications or sequelae of infection due to *Scedosporium* spp. or *L. prolificans*.

Antifungal susceptibilities

Twelve (60%), four (36.4%), and four (44.4%) studies reported on the antifungal drug susceptibility profiles of *Fusarium* spp., *Scedosporium* spp., and *L. prolificans* isolates, respectively. The methods are summarized in Supplementary Table 2. Susceptibility data for azoles and other antifungal agents are outlined in Tables 4 and 5.

In most (8/12 [66.6%]) studies examining *Fusarium* spp., the isolates were obtained solely from superficial sites (Supplementary Table 2).[26,35–41] Two studies (16.7%) examined isolates from both superficial sites and deep tissues, including the bloodstream.[42,43] Only one (8.3%) study examined *Fusarium* isolates obtained solely from invasive/deep tissue infection.[5] No origin for the *Fusarium* isolates was reported in one (8.3%) study (Supplementary Table 2).[44]

No clinical breakpoints have been established for *Fusarium* spp., so resistance rates cannot be reported. Median/mode minimum inhibitory concentrations (MIC) or MIC_{90} values were ≥16 mg/l for itraconazole and isavuconazole for the

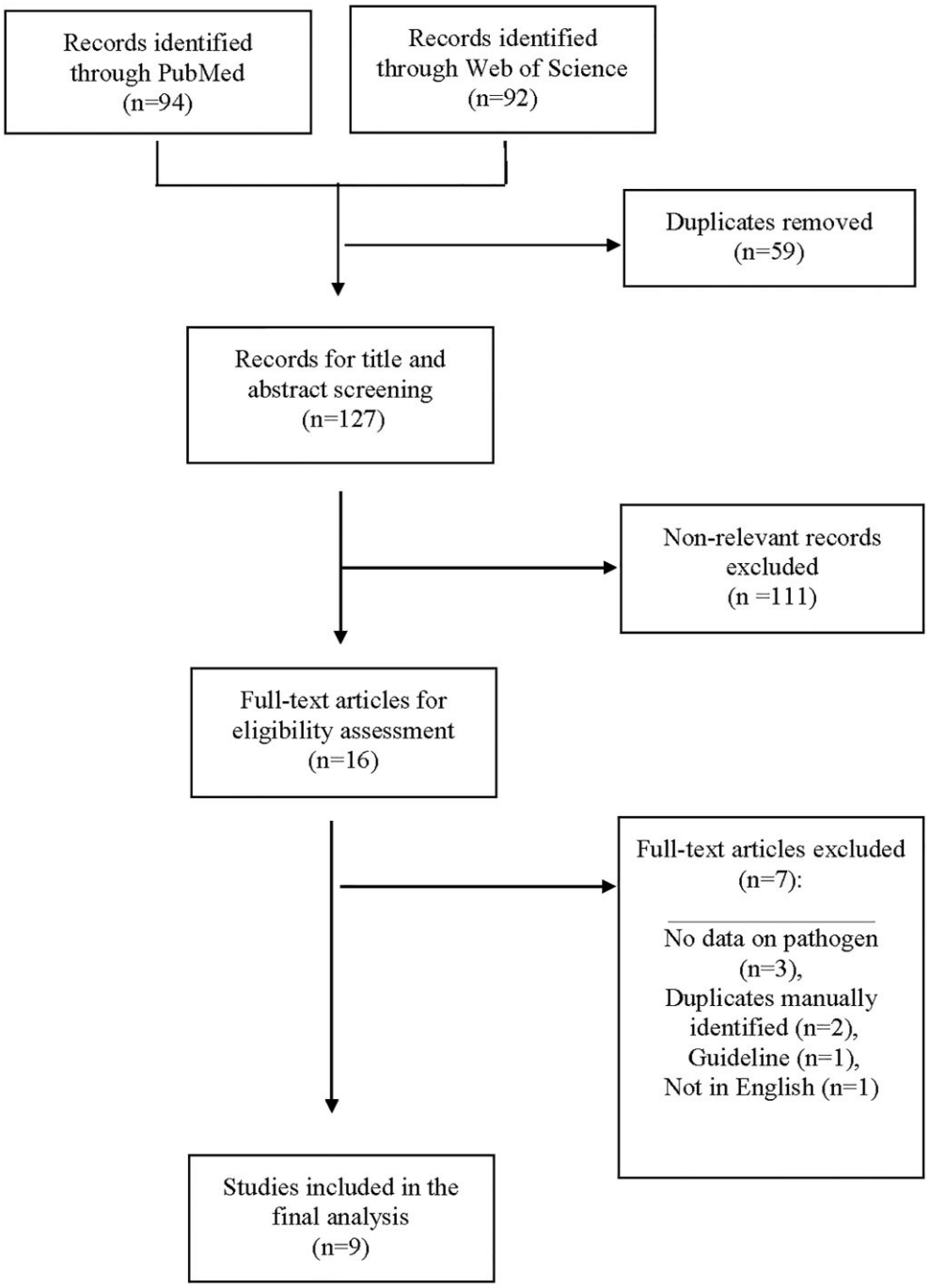

Figure 1c. Flow diagram for selection of studies included in the systematic review of *Lomentospora prolificans*. Based on: Preferred Reporting Items for Systematic Review and Meta-Analyses: The PRISMA Statement.

most common *Fusarium* spp. (Table 4).[5,39,41–43] Overall, median/mode MIC values for voriconazole were higher for *F. solani* SC than for non-*solani Fusarium* spp. (8 mg/l vs. 2–8 mg/l) (Table 4).[36,37,43] Oechsler et al. reported that the median voriconazole MIC value for *F. solani* SC was statistically significantly higher than for non-*solani Fusarium* spp. (16 vs. 4 mg/l; $P < .001$).[35] Posaconazole median/mode MIC values ranged from 8 to 16 mg/l for *F. solani* SC[36,37,43] and were highly variable for non-*solani Fusarium* spp. (0.5–16 mg/l)[36,37,43] (Table 4).

The amphotericin B MIC values for *Fusarium* spp. were comparatively lower than those of azoles, with most (8/12 [66.7%]) studies describing median MIC, mode MIC, and MIC_{90} values of 1–4 mg/l (Table 5).[35–37,39–41,43] There was a trend toward higher median amphotericin B MIC values for *F. solani SC* isolates as compared with non-*solani Fusarium* spp. ($P = .07$) (Table 5).[35] Using our pre-specified criteria, we found very limited susceptibility data on echinocandins. One study reported median minimum effective concentration (MEC) values of 16 mg/l for caspofungin (Table 5).[26,37] Median MIC values were high (>32 mg/l) for flucytosine and variable for natamycin (4–16 mg/l).[35,37,39] Limited data were available for terbinafine, with one study reporting MIC values of 0.5 and 4 mg/l

Table 1. Overall risk of bias for the included studies for *Fusarium* species, *Scedosporium* species, and *Lomentospora Prolificans*.

Author	Year	Risk	Reference
***Fusarium* species**			
Al-Hatmi et al.	2015	Unclear	[85]
Broutin et al.	2020	Unclear	[42]
dos Santos et al.	2020	Unclear	[36]
dos Santos et al.	2019	Unclear	[37]
Espinel-Ingroff et al.	2016	Unclear	[43]
Galletti et al.	2015	Unclear	[38]
Guevara-Suarez et al.	2016	Unclear	[86]
Gupta et al.	2016	High	[26]
Hassan et al.	2016	Unclear	[39]
He et al.	2017	Unclear	[40]
Homa et al.	2013	Unclear	[87]
Manikandan et al.	2019	Unclear	[41]
Oechsler et al.	2013	Low	[35]
Pérez-Nadales et al.	2021	Unclear	[1]
Prajna et al.	2017	Low	[33]
Prajna et al.	2012	Low	[34]
Tortorano et al.	2014	Unclear	[5]
Triest et al.	2015	Unclear	[44]
Varon et al.	2016	Low	[29]
Varon et al.	2014	Low	[30]
***Scedosporium* species**			
Alvarez-Uria et al.	2020	Low	[51]
Bronnimann et al.	2021	Low	[32]
Castanheira et al.	2012	Unclear	[47]
Chang et al.	2019	Low	[52]
Lackner et al.	2014	Unclear	[48]
Lackner et al.	2012	Unclear	[45]
Larcher et al.	2021	Low	[53]
Sedlacek et al.	2015	Unclear	[46]
Seidel et al.	2020	Low	[27]
Slavin et al.	2015	Low	[31]
Vazirani et al.	2021	Low	[2]
Lomentospora prolificans			
Jenks et al.	2020	Low	[68]
Lackner et al.	2011	Unclear	[49]
Schwarz et al.	2019	Low	[54]
Schwarz et al.	2017	Low	[55]
Sedlacek et al.	2015	Unclear	[46]
Seidel et al.	2020	High	[27, 28]
Seidel et al.	2019	High	[28]
Vazirani et al.	2021	Low	[2]
Wu et al.	2020	Unclear	[50]

for *F. oxysporum* SC and *F. solani* SC, respectively (Table 5).[38]

Scedosporium spp. drug susceptibilities were predominantly reported for *S. apiospermum* and *S. boydii* (Tables 4 and 5).[32,45,46] Most (3/4 [75%]) studies were laboratory-based surveillance studies involving North and South America and several European countries (Table 4 and Supplementary Table 2).[45–47] Castanheira et al. compared Clinical and Laboratory Standards Institute with European Committee on Antimicrobial Susceptibility Testing broth microdilution methods and showed highly concordant results between the two methods (essential agreement 96.3%–100%) (Tables 4 and 5).[47]

MIC_{90} values for isavuconazole and itraconazole were ≥16 mg/l and 2 to ≥16 mg/l for *S. apiospermum* and *S. boydii*, respectively (Table 4).[32,45,46] MIC_{90} values for posaconazole were variable and were as high as ≥16 mg/l; although, some studies reported lower values of 2–4 mg/l (Table 4).[32,45,46] Voriconazole showed the lowest MIC_{90} values out of all the azoles tested, ranging from 0.5 to 2 mg/l (Table 4).[32,45,46]

MIC_{50} and MIC_{90} values for amphotericin B were high, mostly ranging between 8 and >16 mg/l for both *S. apiospermum* and *S. boydii* (Table 5). MEC_{90} for the echinocandins was as high as 8–16 mg/l, although lower values (MIC_{90} or MEC_{90} of 1–4 mg/l) were reported in some studies (Table 5).[32,45,46] Lackner et al. observed cross-resistance within *S. apiospermum* and *S. boydii* between the different azoles (Spearman's rank coefficient of 0.37–0.77; $P < .0001$), and between the different echinocandins (Spearman's rank coefficient of 0.66–0.90; $P < .0001$), but not between azoles and echinocandins.[45] Furthermore, Lackner et al. observed two sub-populations of MIC distribution (rather than a normal distribution) for all drugs except voriconazole, and no predictable antifungal resistance pattern between species.[45,48]

Each of the *L. prolificans* antifungal susceptibility studies included small numbers of isolates ranging from 6 to 42, with only two (50%) studies reporting on more than 30 isolates (Tables 4 and 5).[28,46,49,50] Due to the lack of established clinical breakpoints, rates of resistance were not determined, and only MIC or MEC results were reported. Both Wu et al. and

Table 2. Mortality from invasive fungal disease due to *Fusarium* species, *Scedosporium* species, and *Lomentospora prolificans*.

Author	Year	Study design	Study period	Country	Level of care	Population description (*N*)	Number of patients with pathogen (*N*)	Mortality type *n/N* (%)
***Fusarium* species**								
Perez-Nadales et al.[1]	2021	RCS MC	2000–2015	Spain	Tertiary	Patients with invasive fusariosis	58	90-day mortality: Overall mortality: 33/58 (56.9%) Overall mortality statistically significantly higher in neutropenic patients c/w non-neutropenic patients: 38/58 (65.9%) vs. 17/58 (28.6%); $P = .01$
Tortorano et al.[5]	2014	RCS MC	2007–2008	Italy, Serbia, Greece, Czeck/Slovak Republic, Norway, Sweden, Turkey	Tertiary	Patients with hematological malignancy, hematological diseases, HSCT, or solid organ cancer and proven/probable invasive fusariosis	76	30-day mortality: Overall mortality: 22/48 (46%) *Fusarium solani*: 6/9 (66.7%) *Fusarium proliferatum*: 10/16 (62.5%)
Varon et al.[29]	2016	PCS SCS	2008–2014	Brazil	Tertiary	Patients with hematological malignancy, HSCT, or on immunosuppression (211)	211 Observation period: 6/54 (11%) Intervention period:[†] 8/157 (5.1%) No statistically significant difference: ($P = .20$)	30-day mortality: Overall cohort: 12.1% Invasive fusariosis: 6/14 episodes (42.9%) Non-invasive: 23/225 episodes (10.2%) Statistically significant difference: ($P = .003$)
Varon et al.[30]	2014	PCS SCS	2008–2009	Brazil	Tertiary	Patients with hematological malignancy, hematological diseases, HSCT or on immunosuppression (61)	Invasive fusariosis: 6/61 (9.8%)	30-day mortality: Invasive fusariosis: 4/6 (66.7%)

Table 2. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description (*N*)	Number of patients with pathogen (*N*)	Mortality type *n/N* (%)
***Scedosporium* species**								
Bronnimann et al.[32]	2021	RCS MC	2005–2017	France	Tertiary	Patients with proven/probable invasive scedosporiosis or lomentosporiosis* (90)	76	30-day mortality: 7/75 (9.3%) 3-month mortality: 13/70 (18.6%) 3-month mortality significantly higher in patients with malignancy: 15/32 (46.9%) vs. 6/51 (11.8%); $P = .001$
Seidel et al.[27]	2020	RCS MC	1990–2019	Argentina, Australia, Austria, Belgium, Canada, France, Germany, Greece, India, Italy, Mexico, New Zealand, Portugal, Romania, Russia, South Korea, Spain, United Kingdom, United States	NS	Patients ≤18 years with proven/probable invasive scedosporiosis or lomentosporiosis[#] (55)	Invasive *Scedosporium* spp. disease: 33	Overall: 14/33 (42.4%) Day 42: 6/33 (18.2%) Day 42 mortality significantly lower c/w those with invasive *Lomentospora prolificans* disease 6/33 (18.2%) vs. 11/22 (50%); $P = .018$
Slavin et al.[31]	2015	RCS MC	2004–2012	Australia	Tertiary	Patients with proven/probable non-*Aspergillus* mould disease (162)	Invasive *Scedosporium* spp. disease: 25	90-day mortality: 25/54 (46.3%)[$]

Table 2. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description (*N*)	Number of patients with pathogen (*N*)	Mortality type *n/N* (%)
Lomentospora prolificans								
Jenks et al.[68]	2020	RCS MC	January 2008–September 2019	Australia ($n = 17$), United States ($n = 11$), Germany ($n = 8$), Other^ ($n = 5$)	Mixed	Patients proven/probable IFD due to *Lomentospora prolificans*[&]	41	IFD-attributable mortality: 21/40 (52.5%) Statistically significant increase in 28-day survival in those who received combination therapy c/w monotherapy: 15/24 (62.5%) vs. 4/16 (25%); $P = .027$ Statistically significant greater probability of Day 84 and 360 survival in those treated with voriconazole and terbinafine as c/w any other antifungal regimen: Log rank $P = .024$ and .039, respectively
Seidel et al.[27]	2020	RCS MC	1990–2019	Australia, Brazil, France, India, South Korea, Spain, Sweden, United Kingdom, United States	NS	Patients ≤18 years with proven/probable invasive scedosporiosis or lomentosporiosis[#] (55)	*Lomentospora prolificans*: 22	Day 42 mortality in patients with invasive *Lomentospora prolificans* disease: 11/22 (50%) Statistically significantly higher than in those with invasive *Scedosporium* spp. disease: 11/22 (50%) vs. 6/33 (18.2%); $P = .018$ All immunocompromised patients died within 42 days of the diagnosis of invasive disease due to *Lomentospora prolificans*.

Table 2. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description (*N*)	Number of patients with pathogen (*N*)	Mortality type *n/N* (%)
Seidel et al.[28]	2019	RCS MC	January 2000– August 2017	Australia, Japan, United States, Spain, France, Germany, India, Italy, United Kingdom, Brazil, The Netherlands, Poland	Mixed	Patients with proven/probable invasive scedosporiosis or lomentosporiosis[#] (273)	*Lomentospora prolificans* (56)	Day 42 mortality: Immunocompromised: 59% Immunocompetent: 17.6% Statistically significant difference $P = .004$ Day 42 mortality in those with a hematological malignancy: 71.4% 90% of those with a hematological malignancy had fungemia

N, number; *n/N*, number that died/number included; RCS, retrospective cohort study; MC, multicenter; c/w, compared with; vs., versus; HSCT, hematopoietic stem cell transplant; PCS, prospective cohort study; SCS, single-center study; NS, not stated; spp., species; IFD, invasive fungal disease.

[†]If patient had evidence at baseline of skin lesion(s) infected with *Fusarium* species, then patient was started on or changed to voriconazole or posaconazole prophylaxis

[∗]Based on isolates already characterized at National Reference Center for Invasive Mycoses and Antifungals (NRCMA).

[#]Identified from the FungiScope® Registry and from a search of PubMed.

[$]*Scedosporium* species and *Lomentospora prolificans* combined.

[^]Belgium, France, Italy, The Netherlands, and Spain.

[&]Identified from the FungiScope® Registry.

Table 3. Complications and sequelae of infection due to *Fusarium* species.

Author	Year	Study design	Study period	Country	Level of care	Population description (*N*)	Complications and sequelae
dos Santos et al.[36]	2020	RCS MC	2005–2016	NL	NS	Patients with *Fusarium* keratitis (89)	Corneal transplantation: 20 (22.5%) Enucleation/evisceration: 7 (7.8%)
Oechsler et al.[35]	2013	RCS SCS	May 2005–June 2007	USA	Tertiary	Patients with *Fusarium* keratitis (52)	*Fusarium* solani vs. non-*solani Fusarium*: Follow-up BCVA: 20/118 vs. 20/36 Therapeutic penetrating keratoplasty: 7 vs. 0
Prajna et al. [33]	2017	Pre-specified analysis of RCT[#] MC	May 2010–November 2015	India, Nepal, USA	Tertiary	Patients with fungal corneal ulcers and visual acuity ≤20/400 (72/240 culture positive for *Fusarium*) (240)	Corneal perforations: Total: 19 (26.4%) Placebo arm: 12/33 (30.8%) Oral voriconazole arm; 7/39 (17.9%) Therapeutic penetrating keratoplasty: 13/19 (68.4%)
Prajna et al.[34]	2012	Pre-specified analysis of RCT[#] MC	November 2007–May 2008	USA India	Tertiary	Patients with fungal corneal ulcers (120)	*Fusarium* Corneal perforations: Topical voriconazole group: 6/23 (26.1%) Topical natamycin group: 1/21 (4.8%) OR 33.4 (95% CI 1.16–962.9; $P = .041$) Therapeutic penetrating keratoplasty: Topical voriconazole group: 5/6 (83.3%) Topical natamycin group: 1/6 (16.7%)

N, number; RCS, retrospective cohort study; MC, multicenter; NL, Netherlands; NS, not stated; SCS, single-center study; USA, United States of America; BCVA, best corrected visual acuity; RCT, randomized controlled trial; OR, odds ratio; CI, confidence interval.
#Analysis pre-specified in a randomized trial comparing natamycin to voriconazole for the treatment of fungal keratitis ([88])

Table 4. Susceptibility testing of *Fusarium* species, *Scedosporium* species, and *Lomentospora prolificans* to azole antifungal agents.

Author	Year	MIC determination method	Isavuconazole	Itraconazole	Posaconazole	Voriconazole
***Fusarium* species**						
Broutin et al.[42]	2020	EUCAST	*Fusarium fujikuroi:* ($n = 31$) MIC (μg/ml) GM: 13.68 MIC_{50}: >16 MIC_{90}: >16 *Fusarium solani* SC: ($n = 22$) MIC (μg/ml) GM: 14.02 MIC_{50}: >16 MIC_{90}: >16 *Fusarium oxysporum* SC: ($n = 17$) MIC (μmg/ml) GM: 9.41 MIC_{50}: 8 MIC_{90}: >16			
dos Santos et al.*[36]	2020	EUCAST			*Fusarium solani* SC: ($n = 32$) MIC (mg/l) Mode: 16 *Fusarium oxysporum* SC: ($n = 22$) MIC (mg/l) Mode: 16 *Fusarium fujikuroi* SC: ($n = 15$) MIC (mg/l) Mode: 16 Range: 0.25–16	*Fusarium solani* SC: ($n = 32$) MIC (mg/l) Mode: 8 Range: 4–16 *Fusarium oxysporum* SC: ($n = 22$): MIC (mg/l) Mode: 4 Range: 2–16 *Fusarium fujikuroi* SC: ($n = 15$) MIC (mg/l) Mode: 4 Range: 1–8

Table 4. Continued

Author	Year	MIC determination method	Isavuconazole	Itraconazole	Posaconazole	Voriconazole
dos Santos et al.*[37]	2019	EUCAST			*Fusarium solani* SC: ($n = 43$) MIC (mg/l) Median: 16 Range: 8–16 *Fusarium oxysporum* SC: ($n = 24$): MIC (mg/l) Median: 16 Range: 16 *Fusarium fujikuroi* SC: ($n = 16$) MIC (mg/l) Median: 2 Range: 0.25–16 *Fusarium dimerum* SC: ($n = 12$) MIC (mg/l) Median: 16 Range: 1–16	*Fusarium solani* SC: ($n = 43$) MIC (mg/l) Median: 8 Range: 4–16 *Fusarium oxysporum* SC: ($n = 24$): MIC (mg/l) Median: 4 Range: 2–16 *Fusarium fujikuroi* SC: ($n = 16$) MIC (mg/l) Median: 4 Range: 1–8 *Fusarium dimerum* SC: ($n = 12$) MIC (mg/l) Median: 8 Range: 2–8

Table 4. Continued

Author	Year	MIC determination method	Isavuconazole	Itraconazole	Posaconazole	Voriconazole
Espinel-Ingroff et al.[43]	2016	CLSI		*Fusarium solani* SC: (*n* = 338) MIC (μg/ml) Mode: 16 Range: 0.5 to >16 *Fusarium oxysporum* SC: (*n* = 148) MIC (μg/ml) Mode: 16 Range: 1 to >16 *Fusarium verticillioides*: (*n* = 96) MIC (μg/ml) Mode: 16 Range: 1 to >16 *Fusarium proliferatum*: (*n* = 60) MIC (μg/ml) Mode: 16 Range: 1 to >16 *Fusarium dimerum* SC: (*n* = 45) MIC (μg/ml) Mode: 16 Range: 1 to >16 *Fusarium incarnatum–Fusarium equiseti* SC: (*n* = 20) MIC (μg/ml) Mode: 8 Range: 1 to >16	*Fusarium solani* SC: (*n* = 357) MIC (μg/ml) Mode: 8 Range: 1 to >16 *Fusarium oxysporum* SC: (*n* = 148) MIC (μg/ml) Mode: 2 Range: 0.5 to >16 *Fusarium verticillioides*: (*n* = 113) MIC (μg/ml) Mode: 0.5 Range: ≤0.25 to >16 *Fusarium proliferatum*: (*n* = 49) MIC (μg/ml) Mode: 2 Range: 1 to >16 *Fusarium dimerum* SC: (*n* = 48) MIC (μg/ml) Mode: 8 Range: 0.5 to >16 *Fusarium incarnatum–Fusarium equiseti* SC: (*n* = 19) MIC (μg/ml) Mode: 4 Range: 0.5–16 MIC (μg/ml) Range: 0.5 to >16	*Fusarium solani* SC: (*n* = 555) MIC (μg/ml) Mode: 8 Range: 0.5 to >16 *Fusarium oxysporum* SC: (*n* = 200) MIC (μg/ml) Mode: 4 Range: 0.5 to >16 *Fusarium verticillioides:* (*n* = 143) MIC (μg/ml) Mode: 2 Range: 0.5 to >16 *Fusarium proliferatum*: (*n* = 74) MIC (μg/ml) Mode: 4 Range: 1 to >16 *Fusarium dimerum* SC: (*n* = 53) MIC (μg/ml) Mode: 8 Range: 1–16 *Fusarium incarnatum–Fusarium equiseti* SC: (*n* = 20) MIC (μg/ml) Mode: 4 Range: 0.5 to >16 MIC (μg/ml) Range: 1–8
Gupta et al.[#26]	2016	CLSI				

Table 4. Continued

Author	Year	MIC determination method	Isavuconazole	Itraconazole	Posaconazole	Voriconazole
Hassan et al.*[39]	2016	CLSI M38-A2		*Fusarium solani* SC: ($n = 54$) MIC (μg/ml) Median: 16 Range: 2–32		*Fusarium solani* SC: ($n = 54$) MIC (μg/ml) Median: 4 Range: 0.5–8
Manikandan et al.*[41]	2019	CLSI		*Fusarium* spp.: ($n = 200$) MIC (μg/ml) MIC_{50}: 32 MIC_{90}: 32 Range: 4–32		*Fusarium* spp.: ($n = 200$) MIC (μg/ml) MIC_{50}: 4 MIC_{90}: 8 Range: 1–8
Oechsler et al.*[35]	2013	CLSI				*Fusarium solani* ($n = 44$) MIC (μg/ml) MIC_{50}: 16 MIC_{90}: 16 Range: 4 to >16 (on $n = 15$ only) Non-*solani Fusarium* spp. ($n = 14$) MIC (μg/ml) MIC_{50}: 4 MIC_{90}: 4 Range: 2 to >16 (on $n = 12$ only) Statisitcally significant difference in median MIC: 16 vs. 4; $P < .001$

Table 4. Continued

Author	Year	MIC determination method	Isavuconazole	Itraconazole	Posaconazole	Voriconazole
Tortorano et al.[5]	2014	EUCAST		*Fusarium proliferatum:* ($n = 16$) MIC (mg/l) GM: 12.88 MIC_{50}: ≥16 MIC_{90}: ≥16 Range: 1 to ≥16 *Fusarium verticillioides*: ($n = 15$) MIC (mg/l) GM: 1.74 MIC_{50}: 1 MIC_{90}: 2 Range: 1 to ≥16 *Fusarium solani*: ($n = 14$) MIC (mg/l) GM: 16.00 MIC_{50}: ≥16 MIC_{90}: ≥16	*Fusarium proliferatum:* ($n = 16$) MIC (mg/l) GM: 5.91 MIC_{50}: ≥16 MIC_{90}: ≥16 Range: 025 to ≥16 *Fusarium verticillioides*: ($n = 15$) MIC (mg/l) GM: 0.35 MIC_{50}: 0.25 MIC_{90}: 0.5 Range: 0.25–0.5 *Fusarium solani*: ($n = 14$) MIC (mg/l) GM: 13.79 MIC_{50}: ≥16 MIC_{90}: ≥16 Range: 1 to ≥16	*Fusarium proliferatum:* ($n = 16$) MIC (mg/l) GM: 6.44 MIC_{50}: 8 MIC_{90}: ≥16 Range: 2 to ≥16 *Fusarium verticillioides*: ($n = 15$) MIC (mg/l) GM: 1.20 MIC_{50}: 1 MIC_{90}: 2 Range: 0.5–2 *Fusarium solani*: ($n = 14$) MIC (mg/l) GM: 13.12 MIC_{50}: ≥16 MIC_{90}: ≥16 Range: 4 to ≥16
Triest et al.[$44]	2015	EUCAST E.DEF 9.1				*Fusarium oxysporum* SC: ($n = 47$) MIC_{100} (μg/ml) Range: 4 to >16 *Fusarium verticillioides*: ($n = 39$) MIC_{100} (μg/ml) Range: 2 to >16 *Fusarium solani*: ($n = 21$) MIC_{100} (μg/ml) Range: 2 to >16 *Fusarium dimerum* SC: ($n = 17$) MIC_{100} (μg/ml) Range: 4–16 *Fusarium proliferatum*: ($n = 16$) MIC_{100} (μg/ml) Range: 2 to >16

Table 4. Continued

Author	Year	MIC determination method	Isavuconazole	Itraconazole	Posaconazole	Voriconazole
***Scedosporium* species**						
Bronnimann et al.[32]	2021	EUCAST†		*Scedosporium apiospermum*: ($n = 48$) MIC (mg/l) MIC_{50}: 1 MIC_{90}: 16 Range: 0.25–16 *Scedosporium boydii*: ($n = 15$) MIC (mg/l) MIC_{50}: 0.5 MIC_{90}: 2 Range: 0.125–16	*Scedosporium apiospermum*: ($n = 48$) MIC (mg/l) MIC_{50}: 1 MIC_{90}: 2 Range: 0.25–2 *Scedosporium boydii*: ($n = 15$) MIC (mg/l) MIC_{50}: 0.5 MIC_{90}: 16 Range: 0.125–16	*Scedosporium apiospermum*: ($n = 48$) MIC (mg/l) MIC_{50}: 0.5 MIC_{90}: 1 Range: 0.06–2 *Scedosporium boydii*: ($n = 15$) MIC (mg/l) MIC_{50}: 0.25 MIC_{90}: 0.5 Range: 0.25–0.5
Castanheira et al.[47]	2012	CLSI EUCAST		*Scedosporium* spp.: ($n = 63$) MIC/MEC (μg/ml) range: CLSI: 0.5 to >8 EUCAST: 0.5 to >8 %EA: 98.9 *Scedosporium apiospermum*: ($n = 28$) MIC/MEC (μg/ml) range: CLSI: 0.5 to >8 EUCAST: 0.5 to >8 %EA: 96.3	*Scedosporium* spp.: ($n = 63$) MIC/MEC (μg/ml) range: CLSI: 0.5 to >8 EUCAST: 0.5 to >8 %EA: 96.8 *Scedosporium apiospermum*: ($n = 28$) MIC/MEC (μg/ml) range: CLSI: 0.5 to >8 EUCAST: 0.5 to >8 %EA: 96.3	*Scedosporium* spp.: ($n = 63$) MIC/MEC (μg/ml) range: CLSI: 0.25 to >8 EUCAST: 0.25 to >8 %EA: 98.8 *Scedosporium apiospermum*: ($n = 28$) MIC/MEC (μg/ml) range: CLSI: 0.25 to >8 EUCAST: 0.25 to >8 %EA: 100
Lackner et al.[45]	2012	CLSI M38-A2	*Scedosporium apiospermum*: ($n = 124$) MIC (μg/ml) GM: 7.1 MIC_{50}: 8 MIC_{90}:16 Range: 1 to >16 *Scedosporium boydii*: ($n = 44$) MIC (μg/ml) GM: 5.8 MIC_{50}: 8 MIC_{90}: 16 Range: 0.5 to >16	*Scedosporium apiospermum*: ($n = 124$) MIC (μg/ml) GM: 15.3 MIC_{50}: >16 MIC_{90}: >16 Range: 0.25 to >16 *Scedosporium boydii*: ($n = 44$) MIC (μg/ml) GM: 11.8 MIC_{50}: >16 MIC_{90}: >16 Range: 0.125 to >16	*Scedosporium apiospermum*: ($n = 124$) MIC (μg/ml) GM: 2.0 MIC_{50}: 1 MIC_{90}: >16 Range: 0.25 to >16 *Scedosporium boydii*: ($n = 44$) MIC (μg/ml) GM: 1.5 MIC_{50}: 1 MIC_{90}: >16 Range: 0.125 to >16	*Scedosporium apiospermum*: ($n = 124$) MIC (μg/ml) GM: 0.9 MIC_{50}: 1 MIC_{90}: 2 Range: 0.25 to >8 *Scedosporium boydii*: ($n = 44$) MIC (μg/ml) GM: 0.7 MIC_{50}: 0.5 MIC_{90}: 2 Range: 0.125–2

Table 4. Continued

Author	Year	MIC determination method	Isavuconazole	Itraconazole	Posaconazole	Voriconazole
Sedlacek et al.[¶46]	2015	CLSI M38-A2[‡]		*Scedosporium apiospermum*: ($n = 52$) MIC (μg/ml) GM: 10.3 MIC_{90}: >16 Range: 1 to >16 *Scedosporium boydii*: ($n = 34$) MIC (μg/ml) GM: 7.8 MIC_{90}: >16 Range: 1 to >l 16	*Scedosporium apiospermum*: ($n = 52$) MIC (μg/ml) GM: 2.6 MIC_{90}: >16 Range: 0.5 to >16 *Scedosporium boydii*: ($n = 34$) MIC (μg/ml) GM: 1.8 MIC_{90}: 4 Range: 0.5 to >16	*Scedosporium apiospermum*: ($n = 52$) MIC (μg/ml) GM: 1.05 MIC_{90}: 2 Range: 0.5–4 *Scedosporium boydii*: ($n = 34$) MIC (μg/ml) GM: 0.85 MIC_{90}: 1 Range: 0.5–2
Lomentospora prolificans						
Lackner et al.[49]	2011	CLSI M38-A2	($n = 34$) MIC (μg/ml) GM: 5.8 MIC_{50}: 8 MIC_{90}: 16 Range: 0.5 to >16	($n = 34$) MIC (μg/ml) GM: 5.8 MIC_{50}: 8 MIC_{90}: 16 Range: 0.5 to >16	($n = 34$) MIC (μg/ml) GM: 5.8 MIC_{50}: 8 MIC_{90}: 16 Range: 0.5 to >16	($n = 34$) MIC (μg/ml) GM: 5.8 MIC_{50}: 8 MIC_{90}: 16 Range: 0.5 to >16
Sedlacek et al.[¶46]	2015	CLSI M38-A2[‡]		($n = 12$) MIC (μg/ml) GM: 32.0 MIC_{90}: >16 Range: >16	($n = 12$) MIC (μg/ml) GM: 32.0 MIC_{90}: >16 Range: >16	($n = 12$) MIC (μg/ml) GM: 30.2 MIC_{90}: >16 Range: 16 to >16
Seidel et al.[28]	2019	CLSI EUCAST		($n = 11$) MIC (mg/l) Median: 16 IQR: 16–32	($n = 10$) MIC (mg/l) Median: 32 IQR: 28–32	($n = 17$) MIC (mg/l) Median: 8 IQR: 6–16
Wu et al.[50]	2020	CLSI	($n = 42$) MIC (μg/ml) GM: 28.51 MIC_{50}: >16 MIC_{90}: >16 Median: >16 Mode: >16	($n = 42$) MIC (μg/ml) GM: 30.97 MIC_{50}: >16 MIC_{90}: >16 Median: >16 Mode: >16	($n = 42$) MIC (μg/ml) GM: 30.45 MIC_{50}: >16 MIC_{90}: >16 Median: >16 Mode: >16	($n = 42$) MIC (μg/ml) GM: 27.48 MIC_{50}: >16 MIC_{90}: >16 Median: >16 Mode: >16

Data reported as it appears in the source papers.
MIC, minimum inhibitory concentration; EUCAST, European Committee on Antimicrobial Susceptibility Testing; SC, species complex; *n*, number; GM, geometric mean; MIC_{50}, MIC required to inhibit the growth of 50% of isolates; MIC_{90}, MIC required to inhibit the growth of 90% of isolates; CLSI, Clinical and Laboratory Standards Institute; spp., species, MIC_{100}, 100% inhibitory concentration; MEC, minimum effective concentration; %EA, % essential agreement ($\pm 2\log_2$ dilutions); IQR, interquartile range.
*Fungal keratitis isolates only.
#Nail samples only.
$For itraconazole and posaconazole all isolates tested had MIC_{100} higher than the maximum concentration tested (i.e., >16 μg/ml).
†With modifications.[88]
¶Respiratory specimens from cystic fibrosis patients.
‡Modified reading time when the growth control was positive (most often after 48 h of incubation).

Table 5. Susceptibility testing of *Fusarium* species, *Scedosporium* species, and *Lomentospora prolificans* to other antifungal agents.

Author	Year	MIC determination method	Anidulafungin	Caspofungin	Micafungin	Amphotericin B	Terbinafine
***Fusarium* species**							
dos Santos et al.*[36]	2020	EUCAST				*Fusarium solani* SC: ($n = 32$) MIC (mg/l) Mode: 2 Range: 0.5–16 *Fusarium oxysporum* SC: ($n = 22$) MIC (mg/l) Mode: 2 Range: 0.25–16 *Fusarium fujikuroi* SC: ($n = 15$) MIC (mg/l) Mode: 2 Range: 1–4	
dos Santos et al.*[37]	2019	EUCAST		*Fusarium solani* SC: ($n = 43$) MEC (mg/l) Median: 16 Range: 0.5–32 *Fusarium oxysporum* SC: ($n = 24$) MEC (mg/l) Median: 16 Range: 0.063–32 *Fusarium fujikuroi* SC: ($n = 16$) MEC (mg/l) Median: 16 Range: 16 *Fusarium dimerum* SC: ($n = 12$) MEC (mg/l) Median: 16 Range: 2–16		*Fusarium solani* SC: ($n = 43$) MIC (mg/l) Median: 2 Range: 0.063–16 *Fusarium oxysporum* SC: ($n = 24$) MIC (mg/l) Median: 2 Range: 0.25–16 *Fusarium fujikuroi* SC: ($n = 16$) MIC (mg/l) Median: 2 Range: 0.5–8 *Fusarium dimerum* SC: ($n = 12$) MIC (mg/l) Median: 1 Range: 0.125–2	

Table 5. Continued

Author	Year	MIC determination method	Anidulafungin	Caspofungin	Micafungin	Amphotericin B	Terbinafine
Espinel-Ingroff et al.[43]	2016	CLSI				*Fusarium solani* SC: ($n = 608$) MIC (μg/ml) Mode: 2 Range: ≤0.25–16 *Fusarium oxysporum* SC: ($n = 226$) MIC (μg/ml) Mode: 2 Range: ≤0.25–16 *Fusarium verticillioides*: ($n = 151$) MIC (μg/ml) Mode: 2 Range: 0.5–16 *Fusarium proliferatum*: ($n = 82$) MIC (μg/ml) Mode: 2 Range: ≤0.25 to >16 *Fusarium dimerum* SC: ($n = 50$) MIC (μg/ml) Mode: 1 Range: ≤0.25–16 *Fusarium incarnatum–Fusarium equiseti* SC: ($n = 20$) MIC (μg/ml) Mode: 4 Range: 0.5–8	

Table 5. Continued

Author	Year	MIC determination method	Anidulafungin	Caspofungin	Micafungin	Amphotericin B	Terbinafine
Galletti et al.[#38]	2015	CLSI					*Fusarium oxysporum*: ($n = 70$) MIC (μg/ml): 0.5 *Fusarium solani:* ($n = 61$) MIC (μg/ml): 4 *Fusarium subglutinans:* ($n = 16$) MIC (μg/ml): 0.125
Gupta et al.[#26]	2016	CLSI	MEC (μg/ml) Range: >16	MEC (μg/ml) Range: >16		MIC (μg/ml) Range: 0.5–2	
Hassan et al.[*39]	2016	CLSI M38-A2				*Fusarium solani* SC: ($n = 54$) MIC (μg/ml) Median: 4 Range: 0.5–8	
He et al.[*40]	2017	CLSI				*Fusarium solani* SC: ($n = 51$) MIC (μg/ml) MIC_{50}: 2 MIC_{90}: 4 Range: 0.5–16	
Manikandan et al.[*41]	2019	CLSI				*Fusarium* spp.: ($n = 200$) MIC (μg/ml) MIC_{50}: 1 MIC_{90}: 1 Range: 0.125–8	
Oechsler et al.[*35]	2013	CLSI				*Fusarium solani:* ($n = 44$) MIC (μg/ml) MIC_{50}: 2 MIC_{90}: 2 MIC range: 1 to >16 (on $n = 43$) Non-*solani* *Fusarium* spp.: ($n = 14$) MIC (μg/ml) MIC_{50}: 2 MIC_{90}: 2 MIC range: 1–2 (on $n = 14$) Trend in difference in median MIC: 2 vs. 2; $P = .07$	

Table 5. Continued

Author	Year	MIC determination method	Anidulafungin	Caspofungin	Micafungin	Amphotericin B	Terbinafine
Tortorano et al.[5]	2014	EUCAST				*Fusarium proliferatum*: ($n = 16$) MIC (mg/l) GM: 1.35 MIC_{50}: 1 MIC_{90}: 2 Range: 0.5–4 *Fusarium verticillioides*: ($n = 15$) MIC (mg/l) GM: 2.89 MIC_{50}: 4 MIC_{90}: 4 Range: 2–4 *Fusarium solani*: ($n = 14$) MIC (mg/l) GM: 1.05 MIC_{50}: 1 MIC_{90}: 2 Range: 0.5–2	
Triest et al.[44]	2015	EUCASTE.DEF 9.1				*Fusarium oxysporum* SC: ($n = 47$) MIC_{100} (μg/ml) Range: 2 to >16 *Fusarium verticillioides*: ($n = 39$) MIC_{100} (μg/ml) Range: 2 to >16 *Fusarium solani*: ($n = 21$) MIC_{100} (μg/ml) Range: >16 *Fusarium dimerum* SC: ($n = 17$) MIC_{100} (μg/ml) Range: 1–4 *Fusarium proliferatum*: ($n = 16$) MIC_{100} (μg/ml) Range 4–16	*Fusarium oxysporum* SC: ($n = 47$) MIC_{100} (μg/ml) Range: 4 to >16 *Fusarium verticillioides*: ($n = 39$) MIC_{100} (μg/ml) Range: 0.5 to >16 *Fusarium solani*: ($n = 21$) MIC_{100} (μg/ml) Range: >16 *Fusarium dimerum* SC: ($n = 17$) MIC_{100} (μg/ml) Range: 0.25–1 *Fusarium proliferatum*: ($n = 16$) MIC_{100} (μg/ml) Range: 2 to >16

Table 5. Continued

Author	Year	MIC determination method	Anidulafungin	Caspofungin	Micafungin	Amphotericin B	Terbinafine
***Scedosporium* species**							
Bronnimann et al.[32]	2021	EUCAST[†]		*Scedosporium apiospermum*: ($n = 48$) MIC (mg/l) MIC_{50}: 1 $MIC_{90;}$ 2 Range: 0.5–8 *Scedosporium boydii*: ($n = 15$) MIC (mg/l) MIC_{50}: 1 $MIC_{90;}$ 2 Range: 0.125–2	*Scedosporium apiospermum*: ($n = 48$) MIC (mg/l) MIC_{50}: 0.25 $MIC_{90;}$ 1 Range: 0.125–1 *Scedosporium boydii*: ($n = 15$) MIC (mg/l) MIC_{50}: 0.25 $MIC_{90;}$ 1 Range: 0.125–1	*Scedosporium apiospermum*: ($n = 48$) MIC (mg/l) MIC_{50}: 8 $MIC_{90;}$ 16 Range: 1–16 *Scedosporium boydii*: ($n = 15$) MIC (mg/l) MIC_{50}: 8 $MIC_{90;}$ 16 Range: 8–16
Castanheira et al.[47]	2012	CLSIEUCAST	*Scedosporium* spp.: ($n = 63$) MEC (μg/ml) range CLSI: 1 to >8 EUCAST: 1 to >8 %EA: 100 *Scedosporium apiospermum*: ($n = 28$) MEC (μg/ml) range CLSI: 1–4 EUCAST: 1–4 %EA: 100	*Scedosporium* spp.: ($n = 63$) MEC (μg/ml) range CLSI: 0.5 to >8 EUCAST: 1 to >8 %EA: 96.8 *Scedosporium apiospermum*: ($n = 28$) MEC (μg/ml) range CLSI: 0.5 to >8 EUCAST: 1 to >8 %EA: 96.4		*Scedosporium* spp.: ($n = 63$) MIC (μg/ml) range CLSI: 0.5–4[$] EUCAST: 0.25–4[$] %EA: 100% *Scedosporium apiospermum*: ($n = 28$) MIC (μg/ml) range CLSI: 1–4[$] EUCAST: 0.25–4[$] %EA: 100	
Lackner et al.[45]	2012	CLSI M38-A2	*Scedosporium apiospermum*: ($n = 124$) MEC (μg/ml) GM: 0.9 MEC_{50}: 0.5 MEC_{90}: 8 Range: 0.125 to >8 *Scedosporium boydii*: ($n = 44$) MEC (μg/ml) GM: 1.3 MEC_{50}: 1 MEC_{90}: 4 Range: 0.25 to >8	*Scedosporium apiospermum*: ($n = 124$) MEC (μg/ml) GM: 1.6 MEC_{50}: 1 MEC_{90}: 8 Range: 0.5 to >8 *Scedosporium boydii*: ($n = 44$) MEC (μg/ml) GM: 2.1 MEC_{50}: 2 MEC_{90}: 8 Range: 1 to >8	*Scedosporium apiospermum*: ($n = 124$) MEC (μg/ml) GM: 0.2 MEC_{50}: 0.125 MEC_{90}: 4 Range: 0.006 to >8 *Scedosporium boydii*: ($n = 44$) MEC (μg/ml) GM: 0.4 MEC_{50}: 0.25 MEC_{90}: 8 Range: 0.062 to >8	*Scedosporium apiospermum*: ($n = 124$) MIC (μg/ml) GM: 6.5 MIC_{50}: 8 MIC_{90}: >16 Range: 0.5 to >16 *Scedosporium boydii*: ($n = 44$) MIC (μg/ml) GM: 11.3 MIC_{50}: 16 MIC_{90}: >16 Range: 0.5 to >16	

Table 5. Continued

Author	Year	MIC determination method	Anidulafungin	Caspofungin	Micafungin	Amphotericin B	Terbinafine
Sedlacek et al.[¶46]	2015	CLSI M38-A2[‡]		*Scedosporium apiospermum*: ($n = 52$) MEC (μg/ml) GM: 8.0 MEC_{90}: 16 Range: 0.25–16 *Scedosporium boydii*: ($n = 34$) MEC (μg/ml) GM: 6.7 MEC_{90}: 16 Range: 0.5–16		*Scedosporium apiospermum*: ($n = 52$) MIC (μg/ml) GM: 7.8 MIC_{90}: >16 Range: 1 to >16 *Scedosporium boydii*: ($n = 34$) MIC (μg/ml) GM: 14.7 MIC_{90}: >16 Range: 2 to >16	
Lomentospora prolificans							
Lackner et al.[49]	2011	CLSI M38-A2	($n = 34$) MEC (μg/ml) GM: 2.95 MEC_{50}: 4 MEC_{90}: 8 Range: 0.25 to >8	($n = 34$) MEC (μg/ml) GM: 5.77 MEC_{50}: 8 MEC_{90}: >8 Range: 1 to >8	($n = 34$) MEC (μg/ml) GM: 5.11 MEC_{50}: 8 MEC_{90}: >8 Range: 0.25 to >8	($n = 34$) MIC (μg/ml) GM: 7.83 MIC_{50}: >16 MIC_{90}: >16 Range: 0.062 to >16	
Sedlacek et al.[¶46]	2015	CLSI M38-A2[‡]		($n = 12$) MEC (μg/ml) GM: 11.8 MEC_{90}: 16 Range: 8–16		($n = 12$) MIC (μg/ml) GM: 32 MIC_{90}: >16 Range: >16	
Seidel et al.[28]	2019	CLSIEUCAST			($n = 6$) MIC (mg/l) Median: 24 IQR: 0.9–32	($n = 18$) MIC (mg/l) Median: 16 IQR: 4–16	
Wu et al.[50]	2020	CLSI			($n = 42$) MEC (μg/ml) GM: 8.98 MEC_{50}: >8 MEC_{90}: >8 Median: >8 Mode: >8	($n = 42$) MIC (μg/ml) GM: 20.84 MIC_{50}: >16 MIC_{90}: >16 Median: >16 Mode: >16	($n = 42$) MIC (μg/ml) GM: 125.91 MIC_{50}: >64 MIC_{90}: >64 Median: >64 Mode: >64

Data reported as it appears in the source papers
MIC, minimum inhibitory concentration; EUCAST, European Committee on Antimicrobial Susceptibility Testing; SC, species complex; *n*, number; MEC, minimum effective concentration; CLSI, Clinical and Laboratory Standards Institute; spp., species; MIC_{50}, MIC required to inhibit the growth of 50% of isolates; MIC_{90}, MIC required to inhibit the growth of 90% of isolates; GM, geometric mean; MIC_{100}, 100% inhibitory concentration; %EA, % essential agreement ($\pm 2\log_2$ dilutions), IQR, interquartile range.
*Fungal keratitis isolates only.
#Nail samples only.
†With modifications.[89]
$Higher concentrations not tested (i.e., MIC8, MIC >8).
¶Respiratory specimens from cystic fibrosis patients.
‡Modified reading time when the growth control was positive (most often after 48 h of incubation).

Lackner et al. reported an MIC_{90} of ≥16 mg/l for isavuconazole, itraconazole, posaconazole, voriconazole, and amphotericin B, and ≥8 mg/l for anidulafungin, caspofungin, and micafungin (Tables 4 and 5).[49,50] Wu et al. reported high median and mode MIC and MIC_{90} vales of >64 μg/ml for terbinafine (Table 5).[50]

Risk factors and preventability

Of those with *Fusarium* keratitis, 63%–92.9% were contact lens wearers (Table 6).[35,36] While these studies did not include a control group to confirm the association, one study found that only 12% of the Dutch population wore contact lenses (Table 6).[36] The authors suggest the need for education on the proper use of contact lenses and adherence to recommended cleaning guidelines as preventative measures (Supplementary Table 3).[36] Risk factors for invasive fusariosis include allogeneic HSCT, cytomegalovirus reactivation, and the presence of skin lesion positive for *Fusarium* spp. at baseline (Table 6).[30] A prospective study also observed that prophylaxis with broad-spectrum anti-mould azoles (voriconazole or posaconazole) in hematologic patients with *Fusarium*-positive skin lesions at baseline resulted in significantly lower mortality compared with those who received fluconazole or no prophylaxis (0/6 [0%]) vs. 4/5 [80%]; $P = .01$) (Supplementary Table 3).[29] Non-neutropenic patients with invasive fusariosis are more likely than neutropenic patients to have an underlying condition such as chronic cardiac or pulmonary disease.[1]

Risk factors for invasive scedosporiosis include active malignancy (36% with *S. apiospermum)* or SOT (40% with *S. boydii*) (Table 6).[31,32] Slavin et al. reported higher rates of scedosporiosis in patients who had undergone SOT compared with non-recipients (12/23 [52%] vs. 12/39 [30%]; $P = .039$) (Table 6), although about half of the scedosporiosis cases were caused by *S. prolificans* (now classified as *L. prolificans*).[31] In a pediatric case series, malignancy (adjusted hazard ratio [aHR] 8.33, 95% confidence interval [CI] 1.35–51.40), allogeneic HSCT (aHR 20.31, 95% CI 2.07–199.13), and severe infection (aHR 6.12, 95% CI 1.52–24.66) were associated with an increased risk of mortality in those who had IFD due to *Scedosporium* spp. or *L. prolificans* (Table 6).[27] In a study of lung transplant recipients, prior exposure to an antifungal agent was reported as a risk factor for *Scedosporium* spp. or *L. prolificans* isolation (Table 6).[2] The analysis of risk factors for *L. prolificans* was limited, with only one study reporting that invasive infection was more common in immunocompromised patients (39/56 [69.6%]), especially those with malignancy and more specifically those with acute leukemia (Table 6).[28] There were no data reported on what measures should be used to prevent scedosporiosis/lomentosporiosis.

Annual incidence

No global annual incidence rates for *Fusarium* spp., *Scedosporium* spp., and *L. prolificans* were reported. The data utilized in this review relate to the annual incidence at a population level and were derived from four studies only (Supplementary Table 4).[36,51–53] For *Fusarium* keratitis, a mean annual incidence of 0.45 (range 0–1.5)/million was reported in The Netherlands for the time frame of 2010 to 2016 (Supplementary Table 4).[36] The incidence of hospital admissions with *Scedosporium* infection was derived from two studies (Supplementary Table 4).[51–53] Invasive scedosporiosis occurred at a rate of 0.10 per 10 000 hospital admissions over a 20-year period at a tertiary hospital in Spain,[51] but higher rates were reported more recently from an intensive care unit (ICU) in France (0.3 episodes per 1000 ICU admissions) (Supplementary Table 4).[53] In a Western Australian cohort of lung transplant recipients, the overall incidence of IFD was 2.1 per 100 person-years, with *S. apiospermum* SC (3/13 IFD) the second most common cause of IFD after *Aspergillus* spp. (Supplementary Table 4).[52] We did not find any data on the yearly incidence of *L. prolificans*.

Prevalence, global distribution, and trends

The prevalence of *Fusarium* keratitis ranged from 30.4% to 47% (Supplementary Table 5).[33,39]*Fusarium* accounted for 12.7%–19.8% and 17.8% of onychomycosis cases in Brazil and India, respectively (Supplementary Table 5).[26,38] In hematologic patients in Brazil, the prevalence of fusariosis was (14/239) 5.8% (Supplementary Table 5).[29] In the Netherlands, *Fusarium* keratitis increased from 3 to 5 cases per year between 2010 and 2011 to 20–25 cases per year between 2015 and 2016.[36] At a single center in Brazil, the proportion of onychomycosis due to *Fusarium* spp. was 17.7% in 2011 and then decreased to 12.7% in 2012 before increasing to 19.8% in 2013 (Supplementary Table 5).[38] Pérez-Nadales et al. reported an increasing trend in invasive fusariosis from 0.08 cases/100 000 admissions between 2000 and 2009 to 0.22 cases/100 000 admissions between 2010 and 2015 (Supplementary Table 5).[1]

Invasive scedosporiosis accounted for 3.26% of all IFD in a Spanish study (Supplementary Table 5).[51] In France, 8% of all non-*Candida* and non-*Aspergillus* IFD in ICU patients were due to *S. apiospermum*.[53] A prevalence of 15.2% was detected among non-*Aspergillus* IFD in 15 hospitals in Australia.[31] Two studies, both single center, assessed trends of invasive scedosporiosis (Supplementary Table 5).[2,51] In a 1250-bed tertiary hospital in Spain, cases of invasive scedosporiosis/lomentosporiosis remained stable between 2011 ($n = 0$) and 2017 ($n = 1$).[51] At an Australian tertiary referral center *Scedosporium* spp. and *L. prolificans* was first reported in lung transplant patients in 2014 with 1–9 cases reported each year thereafter (Supplementary Table 5).[2]

The prevalence of *L. prolificans* infections ranged from 1.25% to 9.7%.[2,46,54,55] with rates higher (3.1%–9.7%)[46,54,55] in adults and/or children with CF than in lung transplant recipients (1.25%)[2] (Supplementary Table 5).

Discussion

Fungal infections pose an increasing threat and an ongoing challenge to human health. Humans continue to co-exist with and have exposure to fungi in shared environments through inhalation, ingestion, and cutaneous contact. Among those most vulnerable to IFD are the immunocompromised. The ability to prevent and treat IFD is a pivotal requirement for forwarding the fields of cancer therapy, immunotherapy, and transplantation, as well as complex surgical procedures. Adequate surveillance infrastructure to monitor fungal infection patterns and distribution on national, regional, and global scales is lacking; thus, clinical decisions and assessments of trends are often made based on small studies restricted to a particular population or locality.

The paucity of data available for inclusion in this systematic review of *Fusarium* spp., *Scedosporium* spp., and *L. prolificans* proved a major limitation. Only 336, 163, and 152 cases

Table 6. Risk factors for *Fusarium* species, *Scedosporium* species and *Lomentospora prolificans*.

Author	Year	Study design	Study period	Country	Level of care	Population description (N)	Fungal pathogen (N)	Risk factors
***Fusarium* species**								
dos Santos et al.[36]	2020	RCS MC	2005–2016	NL	NS	Patients with *Fusarium* keratitis (89)	89[#] *Fusarium solani* SC: (32) *Fusarium oxysporum* SC: (22) *Fusarium fujikuroi* SC: (15) *Fusarium dimerum* SC: (7) *Fusarium incarnatum–Fusarium equiseti* SC: (1) *Ambrosia Fusarium* complex: (1)	Contact lens: Overall: 92.9% Especially soft contact lenses: (73% of cohort) C/w non-contact lens wearers: OR 19.8 (95% CI: 9.39–41.87).
Oechsler et al.[35]	2013	RCS SCS	May 2005–June 2007	USA	Tertiary	Patients with *Fusarium* keratitis (52)	58	Contact lens use: Patients with *Fusarium solani* keratitis and contact lens use: 24/38 (63%) Patients with non-*solani Fusarium* keratitis and contact lens use: 9/12 (75%)
Perez-Nadales et al.[1]	2021	RCS MC	2000–2015	Spain	Tertiary	Patients with invasive fusariosis	58	Prognostic factor∗: Persistent neutropenia (90-day mortality): HR 7.08 (95% CI 1.91–26.17; $P < .01$)
Varon et al.[30]	2014	PCS SCS	2008–2009	Brazil	Tertiary	Patients with hematological malignancy, hematological diseases, HSCT or on immunosuppression (61)	Invasive fusariosis: 6/61 (9.8%)	Invasive fusariosis[$]: (6) Allogeneic HCT: ($P = .02$) CMV reactivation: ($P = .002$) Presence of skin lesion positive for *Fusarium* spp. at baseline: ($P = .04$)

Table 6. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description (N)	Fungal pathogen (N)	Risk factors
***Scedosporium* species**								
Bronnimann et al.[32]	2021	RCS MC	2005–2017	France	Tertiary	Patients with proven/probable invasive scedosporiosis or lomentosporiosis[&] (90)	76	Disseminated disease: AML AML vs. other HM: 86% vs. 50% Mortality: Neutropenia: OR 9.97 (95% CI 1.83–54.35); $P = .008$ Disseminated disease: OR 7.00 (95% CI 1.33–36.94); $P = .022$ Lack of antifungal prescription after diagnosis: OR 0.02 (95% CI 0.00–0.20); $P = .008$
Seidel et al.[27]	2020	RCS MC	1990–2019	21 Countries: Europe ($n = 26$), North America ($n = 8$), South America ($n = 4$), Asia ($n = 5$), Oceania ($n = 12$)	NS	Patients ≤18 years with proven/probable invasive scedosporiosis or lomentosporiosis[#] (55)	Invasive *Scedosporium* spp. disease: 33	Mortality[^]: Treatment for malignancy: aHR 8.33 (95% CI 1.35–51.40) Allogeneic HSCT: aHR 20.31 (95% CI 2.07–199.13) Severe infection: aHR 6.12 (95% CI 1.52–24.66)
Slavin et al.[31]	2015	RCS MC	2004–2012	Australia	Tertiary	Patients with proven/probable non-*Aspergillus* mould disease (162)	Invasive *Scedosporium* spp. disease: 25	SOT: c/w non-SOT 12/23 (52.2%) vs. 12/39 (30.2%); $P = .039$
Vazirani et al.[2]	2021	RCS SCS	1995–2019	Australia	Tertiary	Lung transplant recipients (962)	Cultured *Scedosporium* spp. or *Lomentospora prolificans*: 30 Invasive *Scedosporium* spp. disease: 7 Colonization with *Scedosporium* spp.: 5	Prior antifungal prophylaxis/therapy: 19/30 (63%)

Table 6. Continued

Author	Year	Study design	Study period	Country	Level of care	Population description (N)	Fungal pathogen (N)	Risk factors
Lomentospora prolificans								
Bronnimann et al.[32]	2021	RCS MC	2005–2017	France	Tertiary	Patients with proven/probable invasive scedosporiosis or lomentosporiosis[&] (90)	76	Mortality (3 month): *Lomentospora prolificans* OR 6.06 (95% CI 0.91–40.25); $P = .062$[¶]
Seidel et al.[28]	2019	RCS MC	January 2000–August 2017	Multiple	Mixed	Patients with proven/probable invasive scedosporiosis or lomentosporiosis[#] (273)	*Lomentospora prolificans* (56)	Immunocompromised: 39/56 (69.6%) Malignancy: 28/56 (50%) Leukemia: 19/56 (33.9%)

N, number; RCS, retrospective cohort study; MC, multicenter; NL, Netherlands; NS, not stated; SC, species complex; c/w, compared with; OR, odds ratio; CI, confidence interval; SCS, single-center study; USA, United States of America; aHR, adjusted hazard ratio; PCS, prospective cohort study; HSCT, hematopoietic stem cell transplantation; CMV, cytomegalovirus; spp., species; AML, acute myeloid leukemia; HM, hematological malignancy; SOT, solid organ transplant.

[#]A total of 89 isolates were included in the study; 78 were identified by molecular methods, and only these were tested for antifungal susceptibility.

∗Multivariate analysis.

[$]Univariate analysis.

[&]Based on isolates already characterized at National Reference Center for Invasvie Mycoses and Antifungals (NRCMA).

^Does not differentiate between *Scedosporium* and *Lomentospora prolificans* IFD.

[¶]Trend to statistical significance.

were included for each species, respectively. For *Scedosporium* spp. and *L. prolificans*, only retrospective studies were available. This has limited the conclusions we can draw for many of the review criteria. For all three pathogen groups, true global incidence and trends are poorly understood. Although annual incidence is likely low, there are concerning indicators. Cases of invasive fusariosis appear to be increasing, and *Scedosporium* spp. and *L. prolificans* infections have only been detected in an Australian cohort of lung transplant recipients since 2014, but more data are required.[36,51] Of note, most of the included studies only examined one or two of the criteria, and the greatest number of criteria examined by any one study was six.[36] This systematic review provides greater insights into the knowledge gaps than any individual paper has to date. Our findings provide the impetus for the global mycology community to perform systematic surveillance studies to fill the knowledge gaps. This will then allow mycologists to develop evidence-based interventions for improved patient outcomes.

Key to early detection and the implementation of preventative measures is the availability of robust surveillance systems that can detect changes in disease patterns, distribution, and antifungal drug susceptibility. All three fungi included in this review are environmental fungi and opportunistic pathogens; thus, the incidence of IFD is likely determined by both environmental and host factors.[30–32] Climate change appears to be a determinant of geographical range and environmental abundance, as has been reported for other fungi.[56,57] The impact of the widespread use of broad-spectrum antifungal agents on the environmental distribution of *Fusarium*, *Scedosporium*, and *L. prolificans* is not well described but is of concern given the worldwide increase in azole-resistant fungi associated with the ongoing widespread use of agricultural fungicides.[58] On a clinical level, the common use of broad-spectrum antifungal prophylaxis in patients with certain hematologic malignancies or post-transplantation, raises the concern of breakthrough IFD due to more resistant pathogens, such as those examined in this review. There is ongoing scientific debate regarding the validity of these concerns, with some studies reporting a shift in the frequency and etiology of breakthrough IFD in high-risk patients on broad-spectrum antifungal prophylaxis,[52,59] and others documenting no change.[60,61] It is important to note that these reports are restricted to a few geographical regions, and the risk of breakthrough IFD with a rarer fungal species may be a bigger concern in regions with a greater environmental abundance. Host susceptibility to IFD is also evolving. Immunotherapeutic agents, including immune checkpoint inhibitors (ICI) and chimeric antigen receptor T cells (CAR-T), are increasingly being used to directly target cancer cells by enhancing T-cell-mediated killing. The incidence of IFD in patients receiving ICI and CAR-T cell therapy is not well defined. Reports of IFD due to *Fusarium* spp., *Scedosporium* spp., and *L. prolificans* emerging during treatment with ICI and CAR-T cell therapy are sparse.[62–65] However, the risk of IFD certainly increases when immunosuppressants, such as high-dose corticosteroids, are used to treat immunotherapy-related adverse events and cytokine release syndrome.[66,67] Without ongoing reporting and monitoring, the adverse impact of these environmental and host/treatment-related factors on the incidence of IFD may go undetected, squandering the opportunity to develop effective prevention strategies.

For those with IFD, mortality was as high as 42.9%–66.7%,[5,29,30] for fusariosis, 42.4%–46.9%,[31,32] for scedosporiosis, and 50.0%–71.4%,[28,68] for lomentosporiosis. Despite the widespread environmental distribution of these pathogens and presumed high degree of human exposure, cases of invasive disease and mortality were largely restricted to immunocompromised patients, highlighting the critical role of deficient host innate and/or adaptive immune responses in disease pathophysiology. Analyses of risk factors for death were limited. For *Fusarium*, 90-day mortality was highest for those with neutropenia,[1] which confirms the previous observation that 90-day survival is reduced to as low as 4% in those with persistent neutropenia and 0% in those who were receiving concurrent systemic corticosteroids.[69] Fungal factors that contribute to invasion and, consequently, mortality include the ability of *Scedosporium* and *L. prolificans* to undergo adventitial sporulation in host tissue to promote fungal dissemination.[70–72] Disseminated scedosporiosis is a risk factor for mortality (odds ratio [OR] 7.00; 95% CI 1.33–36.94; $P = .022$).[32]

Interpretation of antifungal susceptibility data was limited by the relatively small number of isolates studied, particularly for *Scedosporium* spp. and *L. prolificans*, and the few *Fusarium* spp. that were included. For *Fusarium*, the MIC values of voriconazole and posaconazole were generally lower[36,37,43] than those of amphotericin B,[35–37,39–41,43] and no isolate appeared susceptible to isavuconazole or itraconazole (≥16 mg/l).[5,39,41–43] *Fusarium solani* SC showed reduced susceptibility to voriconazole compared with non-*solani Fusarium* spp. (median MIC 16 vs. 4 mg/l; $P < .001$).[35] The median MIC values for echinocandins, flucytosine, natamycin, and terbinafine were as high as 16 to ≥32 mg/l.[26,35,37–39] However, this was based on limited data, and there was great variability between studies. The voriconazole MIC_{90} values for *Scedosporium* were lowest at 0.5–2 mg/l.[32,45,46] The MIC_{90} values of isavuconazole and itraconazole as well as amphotericin B were high for *S. apiospermum* and *S. boydii* ([2 to ≥16 mg/l] and 8–16 mg/l, respectively),[32,45,46] whereas the MIC values for posaconazole and the echinocandins were variable.[32,45,46] Although antifungal resistance rates for *L. prolificans* could not be determined due to a lack of established clinical breakpoints, currently available antifungal drugs have limited *in vitro* activity, with reported MIC_{90} values of ≥16 mg/l for azoles and amphotericin B and MEC_{90} ≥8 mg/l for echinocandins.[28,46,49,50] The relationship between antifungal MIC values and clinical/mycological outcomes of treatment was not able to be defined for *Scedosporium* spp. and *L. prolificans*. The higher mortality rates seen with IFD due to *F. solani* SC may be due in part to the higher MIC values seen, particularly with voriconazole and amphotericin B;[5,35] however, further data are required. All three species of fungi harbor incompletely understood intrinsic resistance mechanisms, including mutations in the *fks*1 gene, which encodes the catalytic subunit of the β-1,3-glucan synthase, the target of echinocandins, and *CYP*15, leading to reduced affinity of azoles for their target and/or over-expression of efflux pumps.[73–75] Combination antifungal therapy is recommended for *L. prolificans*. This is based on *in vitro* synergy susceptibility data, where combinations, such as voriconazole combined with amphotericin B or an echinocandin or terbinafine combined with itraconazole or voriconazole, appear to have activity and potential for efficacy.[76–78] Of note, none of the studies in this systematic review reported on antifungal synergy. This is likely related to the pre-specified eligibility criteria. Newer antifungal agents in development have *in vitro* activity against these fungi.[79–83]

Olorofim has *in vitro* activity against *Scedosporium* spp. and *L. prolificans*, and fosmanogepix against *Fusarium* spp. and *Scedosporium* spp. Although these agents are being used in certain clinical situations, robust clinical efficacy data are pending with studies ongoing (e.g., NCT03583164 and NCT95421858). In clinical practice, surgical debridement, where possible, is a key component of the management of infections due to *Fusarium* spp., *Scedosporium* spp., and *L. prolificans*. However, data on this and other adjunctive therapeutics, such as modulation of immunosuppression, were not available in the studies included in this systematic review.[84]

Given the challenges associated with treating infections due to *Fusarium* spp., *Scedosporium* spp., and *L. prolificans* and the high mortality related to invasive disease with these fungi, prevention is crucial. The use of mould-active azole (voriconazole or posaconazole) prophylaxis in hematologic patients with a positive baseline culture for *Fusarium* was associated with a reduction in mortality compared with those who received fluconazole or no prophylaxis (0/6 [0%] vs. 4/5 [80%]; $P = .01$) in a small, single-center study from Brazil.[29] However, this finding needs to be further explored in a larger, multicenter trial. There are no data to support antifungal prophylaxis to prevent scedosporiosis and lomentosporiosis. Given the susceptibility profiles of these fungi, most available antifungal agents are unlikely to be effective anyway. Reduction in nosocomial exposure to *Fusarium* spp., *Scedosporium* spp., and *L. prolificans* via use of high-efficiency particulate absorbing filtration, positive pressure ventilation, regular surface cleaning, and regular testing of water may prevent exposure and, thus, invasive disease in high-risk patients. However, the impact of these interventions remains unquantified. Prevention of localized disease is likely simpler for *Fusarium* keratitis, where there is an apparent association with contact lens wearing, and thus education regarding appropriate contact lens use and cleaning is a logical target for prevention.[36]

This systematic review has other limitations besides the scarcity of available data. This includes the study time frame (2011–2021). As a result, not all relevant and important studies would have been captured, which may have affected the findings. The exclusion of conference abstracts and studies that were not in English may have also biased the findings. Publication bias may have played a role in this systematic review. Furthermore, it confined itself to invasive disease and keratitis (*Fusarium*); thus, the epidemiology, burden, and outcomes of other infections due to *Fusarium* spp., *Scedosporium* spp., and *L. prolificans* remain to be determined.

Conclusion

Fusarium spp., *Scedosporium* spp., and *L. prolificans* are fungal pathogens that pose a significant threat to human health, particularly that of immunocompromised patients in whom mortality from invasive disease is high. Both national and global surveillance are needed to understand the annual incidence, global distribution, and trends. Larger, multi-center studies analyzing risk factors and reporting on specific outcomes are required to better assess mortality rates, complications, and sequelae. Treatment with currently available antifungal agents is challenging due to the intrinsic resistance of these pathogens. Further antifungal susceptibility studies should be performed. These should first examine a much larger number of isolates from each subspecies. Subsequent studies should examine new antifungal agents and perform synergy testing. In addition, we should determine if there are any changes over time in MIC/MEC values. Crucially, susceptibility results need to be correlated with clinical outcomes in order to develop clinical breakpoints. Global efforts are required to achieve this. Ideally, treatment strategies should be based on clinical trial evidence; however, given the relative rarity of IFD due to *Fusarium* spp., *Scedosporium* spp., and *L. prolificans*, obtaining these data will also require the combined efforts of mycologists globally.

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Author contributions

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Supplementary material

Supplementary material is available at *Medical Mycology* online.

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Conflict of interest

This manuscript has been prepared in a personal capacity by the authors and reflects their views. The views expressed must not be attributed to the WHO, its Secretariat or its member states.

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