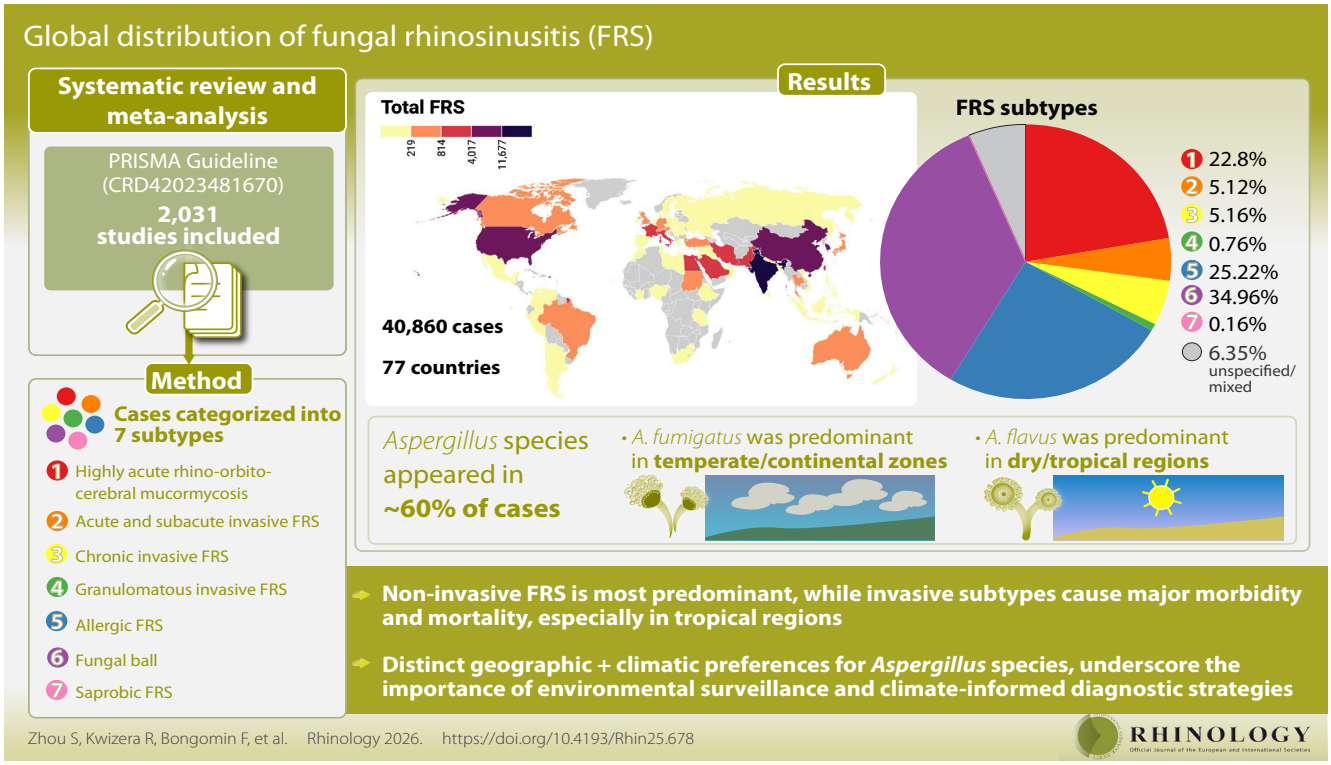
Global distribution of fungal rhinosinusitis

Shaoqin Zhou[1,2,3], Richard Kwizera[4], Felix Bongomin[5,6], Louis Okema[7], Jerom Okot[5], Ervin M. Alcanzo[2], Bassey E. Ekeng[8], Yingqian Kang[1], David W. Denning[6], Sybren de Hoog[1,2,3,9], Sarah A. Ahmed[10]

Rhinology 64: 3, 301 - 311, 2026
https://doi.org/10.4193/Rhin25.678



Abstract

Background: Fungal rhinosinusitis (FRS) comprises subtypes with varying epidemiology and outcomes. Global comparative data remain limited. **Methods**: Following PRISMA guidelines (CRD42023481670), a systematic review and meta-analysis was conducted. Cases were categorized into seven subtypes to assess variation across regions. **Results**: 2,031 studies (40,860 cases, 77 countries) were included. Non-invasive forms accounted for 60% (n=24,582) of cases, mainly fungal ball (35%, n=14,280) and allergic FRS (25%, n=10,302). Invasive subtypes were more frequent in tropical climates, with the hyperacute rhino-orbito-cerebral mucormycosis predominating. This subtype differed from acute and subacute invasive FRS in risk factors (diabetes and COVID-19 vs. leukemia) and geography. *Aspergillus* species appeared in ~60% of cases: *A. fumigatus* dominated in temperate/continental zones, while *A. flavus* was frequent in dry/tropical regions. Non-invasive FRS showed high surgical cure rates (>64%), whereas invasive forms had substantial morbidity and mortality. **Conclusions**: FRS represents a substantial yet underrecognized global health concern. Non-invasive forms are predominating, while invasive subtypes cause major morbidity and mortality, especially in tropical regions. Notably, our findings reveal distinct geographic and climatic preferences for *Aspergillus* species: *A. fumigatus* in temperate/continental zones and *A. flavus* in dry/tropical regions. This ecological divergence underscores the importance of environmental surveillance and climate-informed diagnostic strategies.

Key words: fungal rhinosinusitis epidemiology, acute and subacute invasive FRS, hyperacute rhino-orbito-cerebral mucormycosis, fungal ball, allergic FRS

Introduction

Fungal rhinosinusitis (FRS) is a spectrum of diseases resulting from inflammation of the lining mucosa of the paranasal sinuses triggered by environmental fungal opportunists [1]. This spectrum ranges from simple colonization of the nose and sinuses to more severe manifestations, including acute invasive and fatal inflammatory diseases that may extend into the orbit and brain [2]. Orbital and intracranial extension has been reported in 2–30% of coronavirus disease – 2019 (COVID-19)–associated mucormycosis (CAM) cases in India, with a mortality rate of approximately 42.6% [3-5]. Similarly, high rates of cerebral involvement (up to 27.8%) and orbital invasion (over 80.6%) were observed in acute invasive FRS (AIFRS) cases in Egypt [6].

Currently, the commonly accepted classification, as suggested by a consensus workshop [2, 7-8], is based on histopathological evidence of tissue invasion [9], clinical time-course, and host factors (Table 1). Invasive FRS (IFRS) includes hyperacute rhino-orbito-cerebral mucormycosis (development within a few days), sub-/acute invasive (development within four to 12 weeks), chronic invasive (development over 12 weeks) [10], and granulomatous FRS, whereas non-invasive types include allergic FRS (AFRS), fungal ball (FB, also incorrectly referred to as mycetoma) [2, 11-13], and saprobic colonization (Table 1). Pathologically, invasive disease usually begins in the nasal mucosa and extends into the paranasal sinuses, and in severe cases may progress to the orbit or brain (rhino-cerebral mycosis) [14-18]. Mucoralean agents are hyperacute, in that they develop severe symptoms within a week, while other fungi are subacute or chronic [19]. AFRS involves an immunological response to fungal antigens characterized by eosinophilic infiltration and the formation of nasal polyps [2]. FB, on the other hand, is a non-invasive form of FRS characterized by the colonization of the sinus cavities with compact fungal masses [20]. Classification of FRS is well-documented in published literature, and is important for accurate prognosis and for guiding therapy [21].

While FRS was historically perceived as an uncommon condition [22], the rise in its global burden is predominantly attributed to the growing population of immunocompromised individuals. While in Europe and North America severe mucormycosis was highly exceptional, associated with uncontrolled diabetes, the outbreak of CAM in India has changed our perspective. The incidence rate of over 50,000 CAM cases in India was more than 10 times that of other countries [23,24]. This indicates that FRS potentially exerts a substantial burden in arid and tropical regions. In India, approximately 1.5 million total FRS cases annually are reported, with mucormycosis accounting for about 195,000 cases [25]. Similarly, Sudan has an estimated incidence of 200 FRS cases per 100,000 population [26]. An elevated incidence rate has also been observed beyond tropical regions, evidenced by 392 cases per 100,000 individuals documented in Turkey [27]. Apart from the escalating incidence, a notable concern arises from the high potential mortality rate of invasive forms, reaching up to approximately 50% of patients with IFRS [28].

The predominant fungal culprits of all forms of FRS, in addition to Mucorales (*Mucor, Rhizopus arrhizus, R. oryzae*) in hyperacute FRS, include *Aspergillus* spp., with *A. flavus* emerging as the primary agent in other forms of FRS, particularly in the arid climate of Sudan [29]. Additionally, *Fusarium*, *Scedosporium*, and dematiaceous fungi contribute significantly to other forms of FRS, except for the hyperacute form [30-32]. Clinical presentation of acute or hyperacute FRS commonly involves a constellation of symptoms such as facial pain, nasal congestion, running nose, and headache, and later individuals may experience paralysis of ocular muscles and brain involvement as the condition progresses [1, 33-34].

The management of FRS poses a formidable challenge, particularly for patients with IFRS, with a limited survival rate, ranging from 20% (lowest in those with leukemia) to 80% (highest in diabetic patients) [28].

Despite the growing awareness of FRS, data on its global incidence, prevalence and geographical distribution are still insufficient. Furthermore, much of the research focuses on treatment and outcomes for IFRS, while data on the prevalence and burden of non-invasive forms such as AFRS and FB are lacking. There is also limited understanding of how regional factors—such as climate, healthcare infrastructure, and the prevalence of chronic diseases—affect the distribution and severity of FRS. This study addresses these gaps by synthesizing data from various studies worldwide, providing a clearer picture of the global distribution of FRS. In addition, it offers valuable insights into the various risk factors, causative agents, and treatment outcomes for different FRS subtypes.

Materials and methods

Study design, protocol and registration

This is a quantitative systematic review and it adhered to the relevant sections of the Preferred Reporting Items for a Systematic Review and Meta-analysis (PRISMA) guidelines [35] (Supplementary 1), ensuring transparency, rigor, and reproducibility in the research process. The systematic review protocol was registered in PROSPERO (No. CRD42023481670)

Search strategy and eligibility

We systematically searched for peer-reviewed literature on global FRS, focusing on epidemiology, clinical aspects, and outcomes. The search strategy included articles in English from inception to January 2024. An example search strategy developed for PubMed included the following three core concepts: Concept 1. Fungal infections; Concept 2. (Rhino)sinusitis; Concept 3. Human. Searches were conducted across multiple databases, including Medline through PubMed, Google Scholar, Web of Science, Scopus, Embase, PsycINFO, Global Health, Cochrane Library, and

Table 1. The categories of fungal rhinosinusitis [2,15,54].

Type of FRS		Characteristics
Type 1	Highly acute rhino-orbito-cerebral mucormycosis	The disease is described by a time course of <4 weeks with predominant vascular invasion occurring in patients with immunocompromised status. The histopathology demonstrates hyphal invasion of blood vessels, which may include the carotid arteries and cavernous sinuses, vasculitis with thrombosis, hemorrhage, tissue infarction, and acute neutrophilic infiltrates. Causative agents are mainly *Aspergillus* spp. The infection can start from nasal cavity to cerebral within few days and cause fatal results.
Type 2	Acute and subactute invasive FRS	Causative agents are Mucorales.
Type 3	Chronic invasive FRS	This type is a slowly destructive process that most commonly affects the ethmoid and sphenoid sinuses but may involve any paranasal sinus. The disease typically has a time course of >3 months.
Type 4	Granulomatous invasive FRS	The disease is described by a time course of more than 3 month with an enlarging mass in the cheek, orbit, nose, and paranasal sinuses in immunocompetent hosts. Proptosis is often a prominent feature. Histopathologically, a granulomatous response is seen with considerable fibrosis. Noncaseating granuloma with foreign body or Langhans-type giant cells may be seen, sometimes with vasculitis, vascular proliferation, and perivascular fibrosis.
Type 5	Allergic FRS	Bent and Kuhn [11] proposed five diagnostic criteria: type I hypersensitivity, nasal polyposis, characteristic findings on CT scan, presence of fungi on direct microscopy or culture, and allergic mucin containing fungal elements without tissue invasion.
Type 6	Fungal ball	Fungal ball is described as the presence of noninvasive accumulation of dense conglomeration of fungal hyphae in one sinus cavity, usually the maxillary sinus, although the disease may affect other sinuses or rarely multiple sinuses.
Type 7	Saprophytic FRS	Asymptomatic colonization of mucous crusts within the nasal cavity, often in patients who had previous sinus surgery, has been described as saprophytic fungal infestation.

Health Technology Assessment Database. Full search strategies for all databases were provided (Supplementary 2).

The inclusion criteria were studies that investigated human cases of FRS, regardless of age, exploring risk factors, clinical features, diagnostics, etiology, and treatments. Studies not meeting these criteria, and articles with insufficient data were excluded.

Study selection and data extraction

All stages of the review—screening, full-text assessment, data extraction, and bias assessment—were performed independently by two reviewers (Group A: Sarah A. Ahmed and Ervin M. Alcanzo; Group B: Felix Bongomin and Shaoqin Zhou; Group C: Richard Kwizera and Jerom Okot). Discrepancies were resolved through consensus or by consulting a third reviewer (Shaoqin Zhou). We utilized DedupendNote (http://dedupendnote.nl/) for removing duplicates and Rayyan (https://rayyan.ai/) for title and abstract screening.

Data were extracted using a predefined extraction form (Supplementary 3), which included the following categories: publication year, study design, sample size, patient demographics (sex, age, origin), FRS subtype (Table 1), diagnostic methods, causative agents, mortality rates, treatments, and treatment-related side effects. To ensure consistency across included studies, we reclassified FRS subtypes according to a standardized scheme based on Chakrabarti et al. and Montone et al. (Table 1) [2,8,15,36], comprising seven distinct subtypes. When studies used different terminology or classification systems, cases were re-assigned based on detailed clinical, pathological, and radiographic descriptions. Two reviewers independently performed classification, and discrepancies were resolved by consensus or third-party arbitration.

Methodological quality assessment

We assessed the methodological quality of each study using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists for Case Report [37]. Studies were considered of sufficient quality if they met the following criteria: 1) adherence to inclusion criteria for FRS, 2) clear reporting of sample sizes and identifiable subtypes of FRS. For studies where symptom duration was not mentioned, we classified cases as hyperacute subtype if the causative agents were identified as Mucorales and the outcome was severe, in line with the typical rapid progression of hyperacute FRS, 3) sufficient demographic information, and 4) clear description of diagnostic and treatment approaches. Duplicate publications were identified by cross-referencing study location, time period, patient demographics, and author lists. When possible, duplication was suspected, only the most comprehensive record was retained.

Data analysis and statistics

The analysis involved calculating the number of cases per subtype using Microsoft Excel (v 16.77.1). The total number of disease cases was extracted from all relevant studies (Supplementary 3). For each FRS subtype, the heatmap values were listed in the legend for geographic mapping, which was created using Datawrapper (https://www.datawrapper.de/). Climate

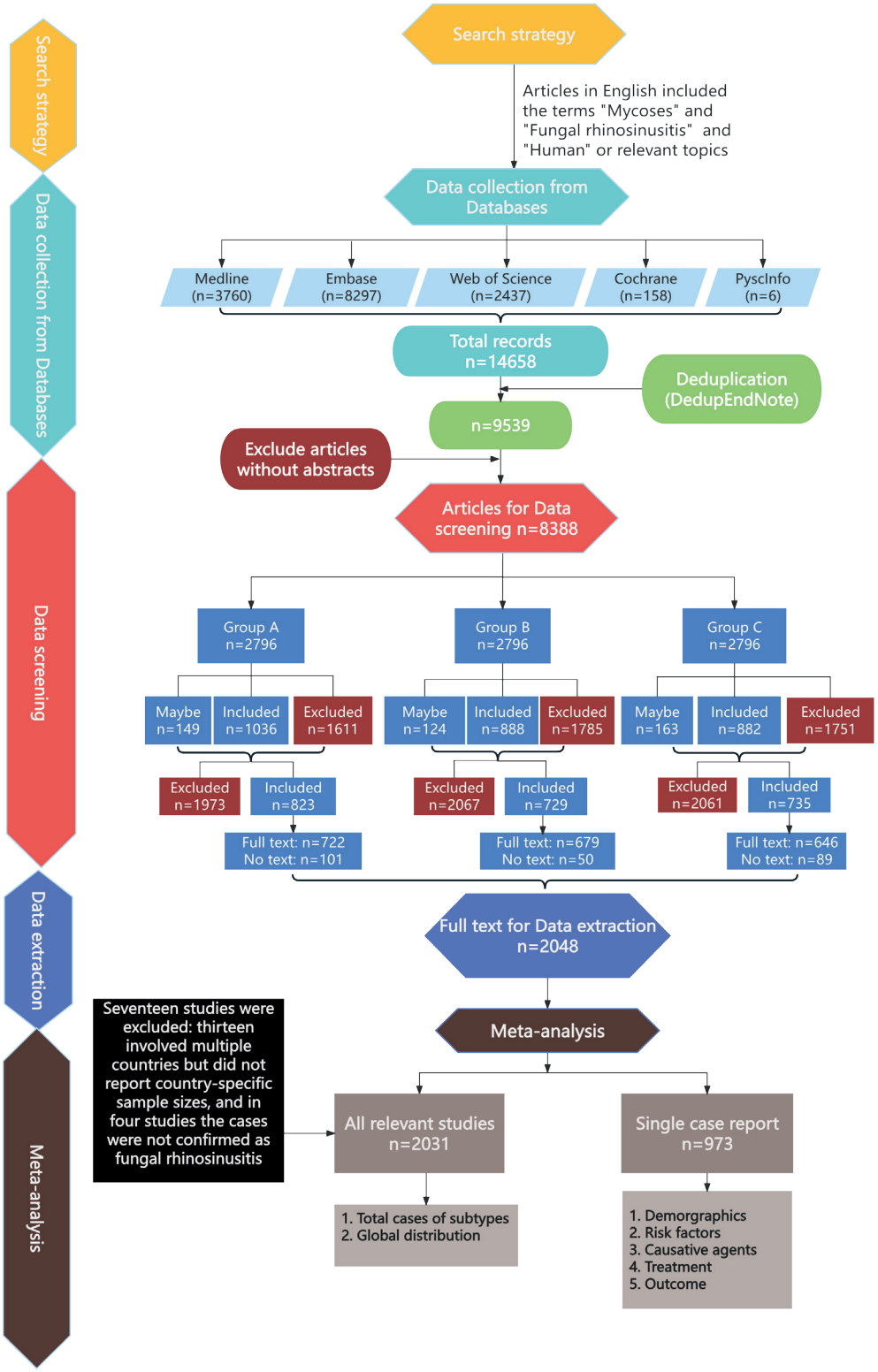


Figure 1. PRISMA flow chart describing the study selection process. The flow diagram illustrates the systematic review process, starting with 14,658 initial records identified from multiple databases: 3,760 from MEDLINE, 8,297 from Embase, 2,437 from Web of Science, 158 from Cochrane, and 6 from PsycInfo. After deduplications, 9,539 records were left. Of these, 1,151 were excluded as they did not contain abstracts, leaving 8,388 that were used for screening. Finally, 6,101 were excluded as they don't meet the objectives of this systematic review, leaving 2,287 records, and among them, 2,048 records with full text were included for eligibility assessment. After further evaluation, 2,031 full texts were included for the global distribution of FRS. Among these, 973 case reports contained complete information on demographics, risk factors, causative agents, and outcomes. These were used to analyse relationship between the variables and each FRS subtype.

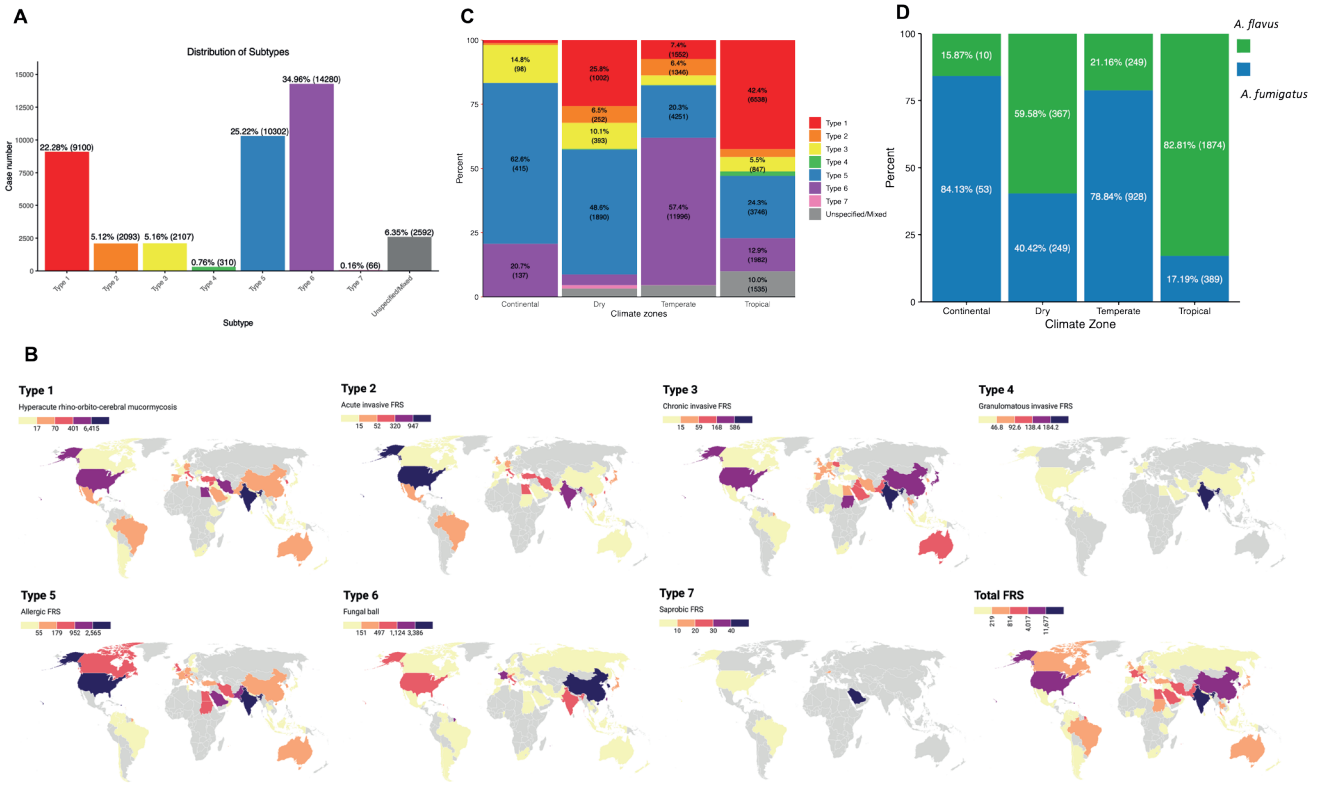


Figure 2. Distribution of fungal rhinosinusitis (FRS) subtypes aggregated from 2031 studies published till January 2024. A. Case numbers and proportional distribution for each subtype; B. Global geographic distribution; C. Distribution by climate zone. D. The distribution of *Aspergillus flavus* and *A. fumigatus* based on climate zone. Subtypes include Type 1 (hyperacute rhino-orbito-cerebral mucormycosis), Type 2 (acute and subacute invasive FRS), Type 3 (chronic invasive FRS), Type 4 (granulomatous invasive FRS), Type 5 (allergic FRS), Type 6 (fungal ball), Type 7 (saprobic FRS), Total FRS (including seven subtypes and unspecific or combinations of two subtypes, such as Type 3 and Type 6 or Type 1 and Type 6, etc). Percentage values less than 5% not shown in the column. The grey color of the map represented no cases reported. The number of cases between brackets.

zones were based on the Köppen Climate Classification (https://earthhow.com/koppen-climate-classification/). A meta-analysis was performed on case reports that included complete data on demographics, risk factors, causative agents, outcomes, and side effects. The analysis was conducted using the statistical software R (https://cran.r-project.org/) and the meta package (https://www.metafor-project.org/doku.php).

Additionally, a Chi-square test function in R was conducted to determine whether there were significant differences in the distribution of FRS subtypes across various countries and climate regions. This test was conducted to evaluate if the frequency of each FRS subtype varied significantly, using the chi-square test function in R.

Results

Study selection and characteristics

The study selection process showed that we initially identified 14,658 records, of which 6,270 were excluded due to duplication or absence of abstracts, leaving 8,388 records for screening (Figure 1). After two rounds of screening, 2,031 records from 77 countries were included. Among these, 973 records were single case report and contained complete data on demographics, underlying diseases, causative factors, treatments and outcomes.

Global distribution of fungal rhinosinusitis

A total of 40,860 cases of FRS were identified from 2,031 studies with the first study reported in 1960 till January 2024, included in this analysis. The distribution of FRS subtypes (Figure 2) encompassed case counts, geographic patterns, and climate zone associations. The most frequently reported subtype was Type 6 (fungal ball), accounting for 14,280 cases, followed by Type 5 (allergic FRS) with 10,302 cases (Figure 2A). Non-invasive forms predominated with Types 5 and 6 together constituting 60.2% of all cases. Type 1 (hyperacute rhino-orbito-cerebral mucormycosis) contributed 9,102 cases (22.3%), representing the most prevalent invasive form. Type 2 (acute and subacute invasive FRS) accounted for 2,091 cases (5.1%). Type 3 (chronic invasive FRS) comprised 2,107 cases (5.2%). Less common subtypes included Types 4 (granulomatous invasive FRS) (n=310), and 7 (saprobic FRS) (n=66), which accounted for 1% or less.

A substantial regional heterogeneity was observed (Figure 2B). India, China, South Korea and The United States exhibited the higher distribution overall, particularly for Types 1 (hyperacute

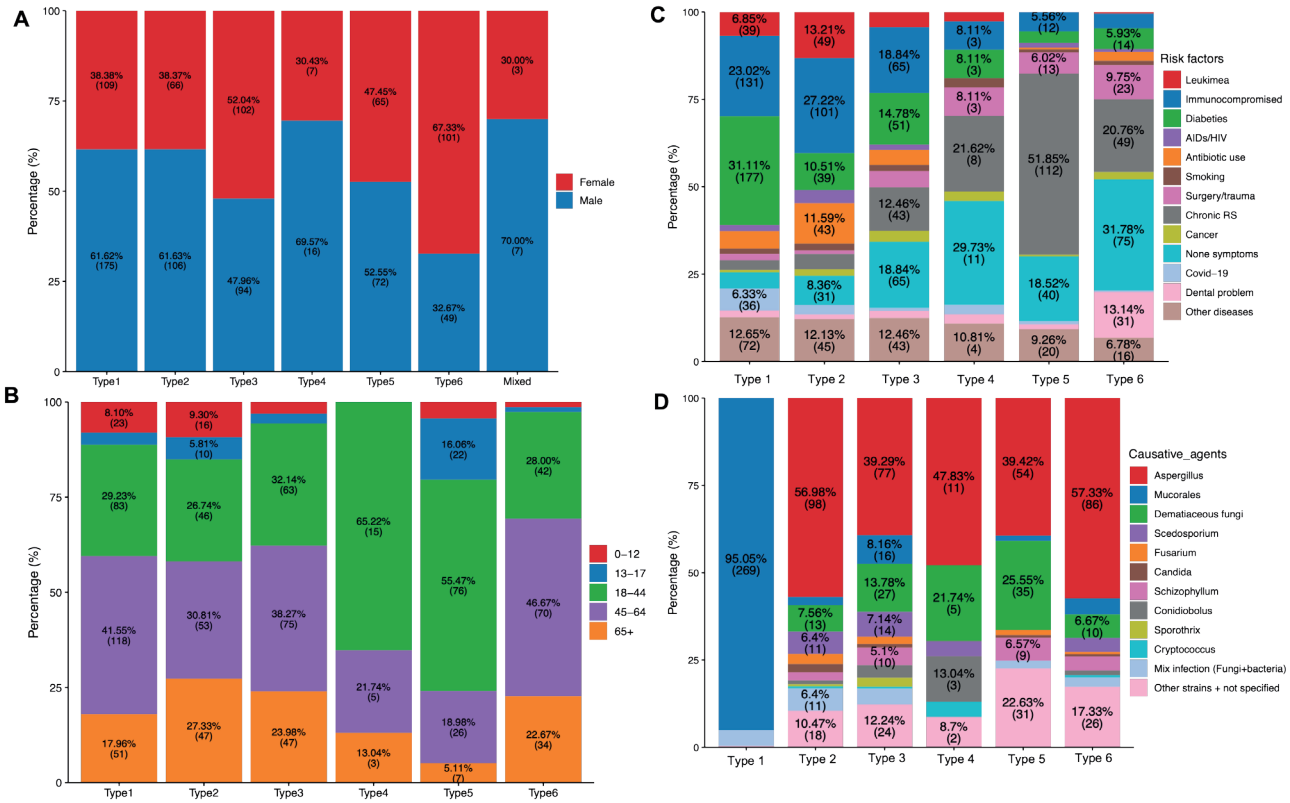


Figure 3. Distribution of FRS subtypes by demographics and potential risk factors. Gender (A), age range (B), risk factor (C), causative agents (D) distribution of fungal rhinosinusitis subtypes. Type 1 (hyperacute rhino-orbito-cerebral mucormycosis), Type 2 (acute and subacute invasive FRS), Type 3 (chronic invasive FRS), Type 4 (granulomatous invasive FRS), Type 5 (allergic FRS), Type 6 (fungal ball). Percentage values less than 5% not shown in the column. The number of cases between brackets.

rhino-orbito-cerebral-mucormycosis), 2 (acute and subacute invasive FRS), 3 (chronic invasive FRS), 4 (granulomatous invasive FRS), 5 (allergic FRS) and 7 (saprobic FRS) in India and Types 1, 2, 3, 5 in The United States. Other regions, including Europe, the Middle East, and East Asia showed average prevalence of each type. By contrast, Africa and South America reported comparatively few cases. A Chi-square test revealed significant differences in the distribution of FRS subtypes across countries ($p < 0.05$). When arranged according to climate zones (Figure 2C), Types 5 and 6 were the predominant forms in temperate regions, together accounting for more than half of all cases. In tropical climates, Type 2 was the most frequent subtype, comprising approximately 40% of cases. Dry climates exhibited a more balanced distribution among several subtypes, while continental climates were characterized by a predominance of Types 5 and 6 and a relatively low frequency of invasive forms. A Chi-square test revealed significant differences in the distribution of FRS subtypes across climate zones ($p < 0.05$).

Based on the species identified in the single case report (n=973), *Aspergillus* was the predominant causative agent (39-57%) among each subtype of FRS (Figure 2D). *Aspergillus flavus* was mainly found in dry and tropical climate regions, accounting for 59.58% and 83.15%, respectively. Whereas *A. fumigatus* was primarily distributed in continental and temperate regions, representing 84.13% and 78.97% of cases, respectively (Figure 2D).

Demographics and risk factors

The distribution of FRS subtypes by demographics and potential risk factors based on 973 single case reports (Figure 3) showed a higher prevalence of Type 6 (fungal ball) in females, with a ratio of 2: 1 among females and males, whereas Types 1 and 2 were more commonly observed in males (Figure 3A). Type 5 (allergic FRS) was more common in younger individuals (≤17 years old), while invasive forms like Types 1, 2, and 3 (chronic invasive FRS) were more prevalent in people above 45 years old (Figure 3B). Regarding potential risk factors (Figure 3C), Types 1 and 2 had a strong association with immunocompromised conditions, while Type 5 was primarily linked to allergy, affecting mainly younger individuals. Types 3 and 4 were associated with chronic diseases and autoimmune disorders, affecting middle-aged to older adults. Type 6 FB was linked to chronic sinusitis, surgery/ trauma, and dental issues. A Chi-square test revealed a significant difference in the distribution of FRS subtypes by gender, age, and

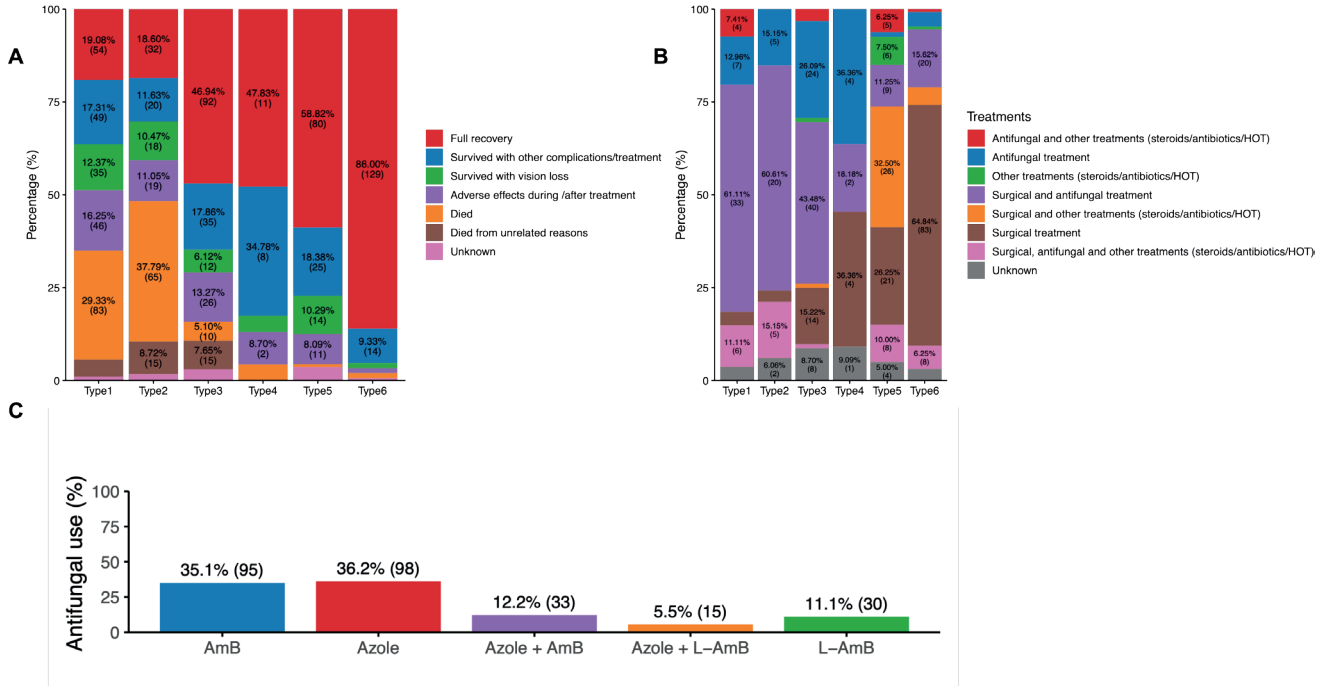


Figure 4. Outcome, and treatment of FRS subtypes. A. Outcome; B. Treatment; C. Antifungal use. Type 1 (hyperacute rhino-orbito-cerebral mucormycosis), Type 2 (acute and subacute invasive FRS), Type 3 (chronic invasive FRS), Type 4 (granulomatous invasive FRS), Type 5 (allergic FRS), Type 6 (fungal ball), Mixed (combinations of two subtypes, such as Type 3 and Type 6 or Type 2 and Type 6, etc.). L-AmB, liposomal amphotericin B. The number of cases in brackets. Adverse effects during/after treatment here only refers to those patients who survived, varying from minor (nausea or skin rash) to serious side effects from the antifungal treatments, and those symptoms were clearly described in the case reports. Full recovery refers to cases where the reports or studies clearly describe the patient's complete recovery with no ongoing adverse effects following treatment. Survival with other complications refers to cases where the patient survived but experienced complications, other than "vision loss" and "adverse effects", which were analyzed separately.

risk factor ($p < 0.05$). Causative agents for different FRS subtypes are dominated by *Aspergillus* species, responsible for nearly 60% of cases, particularly in Types 2 and 6. *Mucoralean* species were almost invariably linked to rapid and aggressive progression, classified in Type 1. *Dematiaceous* fungi more often caused Types 3 and 5 (Figure 3D).

Treatments and outcomes

Full recovery was high in Types 5 and 6 (Figure 4A). For Type 5, surgical intervention or a combination of surgery and other treatments was most frequently applied (Figure 4B). Type 6 was typically managed with surgical treatment alone (Figure 4B). Vision loss was common in Types 1, 2 and 5 (Figure 4A). The mortality rate was high in Types 1 (29%) and 2 (38%) (Figure 4A). For the full recovery cases, multiple treatments were used, the combination of surgical and medical treatments were effective in the majority of cases (Figure 4B). Among antifungal regimens, liposomal-/amphotericin B and azoles were the predominant therapeutic options, accounting for 82.4% of treated cases, while combination therapy with both agents comprised 17.7% (Figure 4C).

Discussion

This systematic review and meta-analysis provide the most comprehensive assessment so far of the global distribution, and clinical characteristics of all forms of FRS. Based on data from 40,438 cases reported across 77 countries, our analysis indicates that FRS has a significant impact worldwide, which may be even greater than previously recognized. Non-invasive forms such as AFRS and FB made up about 60% of all cases. These figures underscore that FRS is not a rare condition but a major global health concern requiring better recognition in public health strategies.

In our study, we listed rhino-orbito-cerebral mucormycosis as Type 1 (hyperacute rhino-orbito-cerebral mucormycosis), being a hyperacute form of FRS. This form is exceptionally aggressive, with infection spreading to the rhino-cerebral region within just a few days. This clinical pattern is caused by fungi belonging to the order Mucorales, and distinguished microbiologically and behaviorally from other acute invasive forms, which progress slightly slower (days to 2-4 weeks) [38]. Full recovery of Types 1 and 2 was less than 20% and the mortality of both types was high at 29% and 38%, respectively. Analysis of associated risk factors showed that Type 2 is more frequently linked to leu-

kemia, and immunosuppressive conditions, whereas Type 1 is commonly associated with diabetes, the use of corticosteroids, and COVID-19 infection ($p< 0.05$). There is evidence suggesting that diabetic patients have better outcomes than those with immunosuppression [39]. Especially during the COVID-19 pandemic, an increasing number of mucormycosis cases were reported worldwide, with India having the highest incidence [23]. These findings highlight the need for heightened vigilance regarding mucoralean fungi, particularly in the context of emerging comorbidities.

Regarding causative agents, *Aspergillus* species were dominant across all six non-mucoralean FRS subtypes. *Aspergillus fumigatus* is the leading pathogen in aspergillosis, particularly pulmonary aspergillosis [40]. In FRS, *A. fumigatus* predominated in continental and temperate regions, while *A. flavus* prevailed in dry and tropical climates, including countries such as Sudan, India, Indonesia and Iran. These distribution patterns likely reflect ecological niches preferred by the respective fungal species [41,42]. *A. fumigatus* has a preference for self-heated biological materials such as compost [43], while *A. flavus* is more prevalent in dry grains and peanuts causing post-harvest deterioration [42, 44]. Their different climatic affinities may influence both exposure risk and regional patterns of disease. The clinical implications of these ecological differences warrant further investigation, particularly regarding antifungal susceptibility and treatment outcomes.

The demographic and clinical patterns observed in this study are broadly consistent with earlier findings [45] but also reveal some finer distinctions in how FRS presents across patient groups. Invasive FRS more frequently affected males and older adults, often in the context of underlying conditions that compromise immune function, including hematologic malignancies, diabetes, and prolonged corticosteroid use. Conversely, AFRS mostly afflicted younger people. Additionally, FB were more common among females and often occurred in patients with chronic sinus problems and preceding dental procedures.

Treatment outcomes were very different for each subtype. As expected, non-invasive forms had high percentages of full recovery, especially when treated surgically. Type 6 (fungal ball) was typically managed with surgical treatment alone, as this infection often concerned a non-invasive mass that could be removed without the need for adjuvant antifungal therapy, resulting in high cure rates (86%). Notably, a recent imaging-based cohort study suggests that incidental, asymptomatic fungal balls in elderly patients may remain stable over years without intervention, indicating that management could be individualized based on symptoms and patient factors [46]. Invasive disease is linked to high rates of morbidity and mortality [47]. Complications are common in both acute and chronic FRS. Importantly, the frequent occurrence of vision loss in both invasive and allergic subtypes underscores the need for early recognition and treatment to prevent irreversible complications. Liposomal amphotericin B is the first-line drug in the management of mucormycosis [48], while voriconazole and echinocandins are inactive [49,50]. The combination of L-AMB with azoles seems to yield better outcomes in all types of infection [51]. However, the combination with surgery was found to be the most effective approach.

In the present strudy, several limitations should be acknowledged. First, despite careful screening, duplication of cases across reports could not be entirely excluded. Second, we relied heavily on case reports and retrospective studies, which may introduce selection and reporting biases. This is particularly evident in regions with limited diagnostic capacity and access to mycology services, such as parts of Africa and South America. The relatively low number of reported cases from these regions may reflect under-reporting rather than a true lower disease burden, influenced by factors such as patients having to pay for diagnostics, limited cross-sectional imaging availability or access to fungal diagnostic services and publication bias. Third, variation in subtype classification and diagnostic criteria across studies may limit comparability. In particular, the lack of molecular confirmation in many older series may have led to misclassification of causative fungi. We attempted to mitigate this through reclassification and standardization where possible. Furthermore, environmental and host factors are dynamic, and estimates may shift with changing immunosuppressive therapies, climate change, and emerging fungal pathogens. Lastly, the predominance of English-language studies may have led to underrepresentation of data from non-English-speaking regions.

Future research should prioritize the development and validation of standardized diagnostic criteria, given the considerable heterogeneity in cases and definitions used in the papers. As example, some authors checked and reported either skin prick testing or serum fungal specific IgE tests and included this in their diagnosis criteria, whereas others inspected the mucus obtained from surgery with stains for fungal hyphae and eosinophils, as features for diagnosis and classification. Accurate diagnosis enables more reliable epidemiological surveillance. Estimates of the regional, national and global burden of FRS subtypes are valuable and methods should be developed to quantify the chronic and acute forms separately in the future. Prospective, multicenter cohort studies with robust follow-up are urgently needed to delineate the true incidence, risk factors, and long-term outcomes of all FRS subtypes. It is essential to explore the ecological, environmental, and evolutionary factors that contribute to features such as the variation between *A. flavus* and *A. fumigatus*. Additionally, investment in affordable rapid diagnostic tools, such as Mucorales PCR and antigen testing and antifungal stewardship programs could substantially improve care in low-resource settings [52,53]. Finally, given the apparent influence of climate and emerging comorbidities such

as COVID-19 and diabetes on FRS burden, coordinated public health strategies and regionally tailored interventions will be essential to mitigate the impact of this complex and evolving group of infections.

Conclusion

Our findings underscore the importance of heightened awareness of clinicians and the integration of multidisciplinary approaches to improve patient prognosis and quality of life worldwide.

Acknowledgements

We thank information specialist Marloes IJff from Radboud University. This work was supported by the 111 Project under Grant (No. D20009); National Natural Science Foundation of China under Grant (No. 32060034, 32460051); International Science and Technology Cooperation Base of Guizhou Province under Grant (No. [2020]4101); Talent Base Project of Guizhou Province, China under Grant [No. RCJD2018-22]; High-level Innovation Talent Project of Guizhou Province under Grant (No. GCC[2022]036-1); Major Science and Technology Projects of China Tobacco under Grant [No. 110202101048(LS-08)]; Foundation of Key Laboratory of Microbiology and Parasitology of Education Department, Guizhou under Grant (No. QJJ [2022] 019); Ministry of Education Project under Grant (No. 07150120711); Guizhou Provincial Basic Research Program under Grant (No. zk[2025]525); and China Scholarship Council under Grant (No. 202108520040).

Author contributions

SZ, FD, SAA, and SdH formulated the research question. SZ, SAA, and SdH designed the study and methods. SZ, RK, JO, EMA, FB, and SAA contributed to the literature review. SZ, RK, JO, EMA, FB, and SAA contributed to data extraction. SZ, SAA and SdH analyzed data. SZ, RK, BEE, FB, SAA, and SdH prepared the first draft of the manuscript. All authors interpreted the results, commented on drafts of the article, and approved the final version.

Conflict of interest

None of the authors of the present manuscript has a commercial or other association that might pose a conflict of interest (e.g., pharmaceutical stock ownership and consultancy).

Funding

None declared.

Supplementary data

Supplementary data to this article can be found online "Figshare" under the link dx.doi.org/10.6084/m9.figshare.30295432.

References

1. Singh V. Fungal rhinosinusitis: Unravelling the disease spectrum. J Maxillofac Oral Surg. 2019;18(2):164-79.
2. Chakrabarti A, Denning DW, Ferguson BJ, et al. Fungal rhinosinusitis: a categorization and definitional schema addressing current controversies. Laryngoscope. 2009;119(9):1809-18.
3. Ravani SA, Agrawal GA, Leuva PA, Modi PH, Amin KD. Rise of the phoenix: Mucormycosis in COVID-19 times. Indian J Ophthalmol. 2021;69(6).
4. Gaurkar SS, Deshmukh PT, Khan FQ. Post COVID rhino-cerebral mucormycosis at a tertiary hospital in Central India: A retrospective cohort study. Egypt J Otolaryngol. 2024;40(1):140.
5. Sharma AK, Nagarkar NM, Gandhoke CS, et al. Rhinocerebral mucormycosis (RCM): To study the clinical spectrum and outcome of 61 cases of RCM managed at a tertiary care center in India. Surg Neurol Int. 2023;14:15.
6. El-Kholy NA, El-Fattah AMA, Khafagy YW. Invasive fungal sinusitis in post COVID-19 patients: A new clinical entity. Laryngoscope. 2021;131(12):2652-8.
7. Chakrabarti A, Das A, Panda NK. Controversies surrounding the categorization of fungal sinusitis. Med Mycol. 2009;47 Suppl 1:S299-308.
8. Lander D, Roland L. Updates in the classification of fungal sinusitis. Curr Treat Opt Allergy. 2023;10:1-13.
9. Deutsch PG, Whittaker J, Prasad SJM. Invasive and non-invasive fungal rhinosinusitis—a review and update of the evidence. Medicina (Kaunas). 2019 Jun 28;55(7):319.
10. Montone KT. Pathology of fungal rhinosinusitis: A review. Head Neck Pathol. 2016;10(1):40-6.
11. Montone K. Recent considerations in the classification and pathogenesis of fungal rhinosinusitis. In Pathobiology of Human Disease, Editor(s): McManus LM, Mitchell RN. Academic Press, 2014,1432-1445, 2014.
12. Romano FR, Anselmo-Lima WT, Kosugi EM, Sakano E, Valera FCP, Lessa M, et al. Rhinosinusitis: Evidence and experience - 2024. Braz J Otorhinolaryngol. 2025;91(5):101595.
13. Hora JF. Primary aspergillosis of the paranasal sinuses and associated areas. Laryngoscope. 1965;75:768-73.
14. Ismaiel WF, Abdelazim MH, Eldsoky I, et al. The impact of COVID-19 outbreak on the incidence of acute invasive fungal rhinosinusitis. Am J Otolaryngol. 2021;42(6):103080.
15. Salehi M, Mahmoudi S, Rezahosseini O, et al. The epidemiological, clinical, mycological, and pathological features of rhino-cerebral mucormycosis: A systematic review. Iran J Pathol. 2022;17(2):112-21.
16. Callejas CA, Douglas RG. Fungal rhinosinusitis: What every allergist should know. Clin Exp Allergy. 2013;43(8):835-49.
17. Anselmo-Lima WT, Lopes RP, Valera FC, Demarco RC. Invasive fungal rhinosinusitis in immunocompromised patients. Rhinology. 2004;42(3):141-4.
18. Raz E, Win W, Hagiwara M, Lui YW, Cohen B, Fatterpekar GM. Fungal Sinusitis. Neuroimaging Clin N Am. 2015;25(4):569-76.
19. Ahmed SA, Alcanzo EM, Li Q, et al. The other black fungi: Exploring the opportunists in the order Pleosporales. One Health Mycology 2025;2(1):11-41.
20. Chakrabarti A, Das A, Panda NK. Overview of fungal rhinosinusitis. Ind J Otolaryngol Head Neck Surg. 2004;56:251-8.
21. Sureshkumar S, Pandian DR, Ganapathy S, Edward IMJ. A clinicopathological study of fungal diseases in patients with chronic rhinosinusitis and sinonasal polyposis. Chennai: Tamilnadu Dr. Mgr Medical University; 2020.
22. Valera FC, do Lago T, Tamashiro E, Yassuda CC, Silveira F, Anselmo-Lima WT. Prognosis of acute invasive fungal rhinosinusitis related to underlying disease.Int J Infect Dis. 2011;15(12):e841-4.
23. Pasquier G. COVID-19-associated mucormycosis in India: Why such an outbreak? J Med Mycol. 2023;33(3):101393.
24. Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. J Fungi (Basel).

2019;5(1).
25. Ray A, Aayilliath KA, Banerjee S, Chakrabarti A, Denning DW. Burden of serious fungal infections in India. Open Forum Infect Dis. 2022;9(12):ofac603.
26. Ahmed SA, Ismail M, Albirair M, Nail AMA, Denning DW. Fungal infections in Sudan: An underestimated health problem. PLoS Negl Trop Dis 2023;17(9) e0011464.
27. Hilmioğlu-Polat S, Seyedmousavi S, Ilkit M, et al. Estimated burden of serious human fungal diseases in Turkey. Mycoses. 2019;62(1):22-31.
28. Raiesi O, Hashemi SJ, Ardehali MM, et al. Molecular identification and clinical features of fungal rhinosinusitis: A 3-year experience with 108 patients. Microb Pathog. 2021;158:105018.
29. Zhou S, Ismail MA, Buil JB, et al. Fungi involved in rhinosinusitis in arid regions: insights from molecular identification and antifungal susceptibility. Microbiol Spectr. 2023;11(5):e01831-23.
30. Jain R, Singhal SK, Singla N, Punia RS, Chander JJM. Mycological profile and antifungal susceptibility of fungal isolates from clinically suspected cases of fungal rhinosinusitis in a tertiary care hospital in North India. Mycopathologia. 2015;180:51-9.
31. Bakhshaee M, Bojdi A, Allahyari A, et al. Acute invasive fungal rhinosinusitis: our experience with 18 cases. Eur Arch Otorhinolaryngol. 2016;273(12):4281-7.
32. Pagella F, De Bernardi F, Dalla Gasperina D, et al. Invasive fungal rhinosinusitis in adult patients: Our experience in diagnosis and management. J Craniomaxillofac Surg. 2016;44(4):512-20.
33. Takhenchangbam DS, Laishram RS, Thoudem TS, Sunita A, Imchen LT. Proptosis and facial palsy as an unusual clinical presentation of acute myeloid leukemia. Iran J Cancer Prev. 2013;6(1):52-4.
34. Monroe MM, McLean M, Sautter N, Wax MK, Andersen PE, Smith TL, et al. Invasive fungal rhinosinusitis: A 15-year experience with 29 patients. Laryngoscope. 2013;123(7):1583-7.
35. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Int J Surg. 2010;8(5):336-41.
36. Bent JP, 3rd, Kuhn FA. Diagnosis of allergic fungal sinusitis. Otolaryngol Head Neck Surg. 1994;111(5):580-8.
37. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. Int J Evid Based Healthc. 2015;13(3):147-53.
38. Sajjan A, Nimbal AV, Shahapur R, Bagoji IB, Chiniwar VA, Chillalashetti SK. Post-COVID-19 rhino-cerebral mucormycosis: An observational study during the second wave. Maedica (Bucur). 2022;17(1):103-6.
39. Watkinson J, Clarke R. Scott-Brown's otorhinolaryngology and head and neck surgery: 3 volume set: CRC Press; 2018.
40. Dagenais TR, Keller NP. Pathogenesis of *Aspergillus fumigatus* in invasive aspergillosis. Clin Microbiol Rev. 2009;22(3):447-65.
41. de Hoog GS GJ, Ahmed SA, Al-Hatmi AMS, Figueras MJ, Vitale RG. Atlas of clinical fungi. 4 ed. Hilversum2025.
42. Zhou S, Ahmed SA, Tehupeiory-Kooreman M, et al. No evidence for environmental triazole resistance selection route in *Aspergillus* section *flavi*, The Netherlands, 1994–2023. Mycopathologia. 2025;190(6):99.
43. Fraaije BA, Atkins SL, Santos RF, Hanley SJ, West JS, Lucas JA. Epidemiological studies of pan-azole resistant *Aspergillus fumigatus* populations sampled during tulip cultivation show clonal expansion with acquisition of multi-fungicide resistance as potential driver. Microorganisms. 2021;9(11).
44. Dobson ADW. Yeasts and molds | *Aspergillus flavus*. In: Fuquay JW, editor. Encyclopedia of dairy sciences (Second Edition). San Diego: Academic Press; 2011. 785-91.
45. Dufour X, Kauffmann-Lacroix C, Ferrie JC, Goujon JM, Rodier MH, Klossek JM. Paranasal sinus fungus ball: Epidemiology, clinical features and diagnosis. A retrospective analysis of 173 cases from a single medical center in France, 1989-2002. Med Mycol. 2006;44(1):61-7.
46. Margulis I, Shopen Y, Zaseeva T, et al. Natural history of incidental paranasal sinus fungal balls: evidence from a decade-long imaging-based cohort. Rhinology. 2025;63(6):716-24.
47. Huang YF, Liang KL, Liang CY, Yang PC, Chen JP, Wei LC. Acute invasive fungal rhinosinusitis-related orbital infection: A single medical center experience. J Ophthalmol. 2021;2021:9987871.
48. Kant Singh N, Hage N, Ramamourthy B, Medha Kappagantu K. COVID-19 associated rhino-orbital-cerebral mucormycosis: A proposed classification and treatment strategies. Infect Disord Drug Targets. 2022;22(8):1-7.
49. Alastruey-Izquierdo A, Castelli MV, Cuesta I, Zaragoza O, Monzón A, Mellado E, et al. In vitro activity of antifungals against Zygomycetes. Clin Microbiol Infect. 2009;15 Suppl 5:71-6.
50. Guinea J, Peláez T, Recio S, Torres-Narbona M, Bouza E. In vitro antifungal activities of isavuconazole (BAL4815), voriconazole, and fluconazole against 1,007 isolates of zygomycete, *Candida*, *Aspergillus*, *Fusarium*, and *Scedosporium* species. Antimicrob Agents Chemother. 2008;52(4):1396-400.
51. Sigera LSM, Denning DW. A systematic review of the therapeutic outcome of mucormycosis. Open Forum Infectious Diseases. 2024;11(1):ofad704.
52. Brown L, Tschiderer L, Alanio A, et al. The diagnosis of mucormycosis by PCR in patients at risk: a systematic review and meta-analysis. EClinicalMed. 2025;81:103115.
53. Rousselot J, Millon L, Scherer E, et al. Detection of Mucorales antigen in bronchoalveolar lavage samples using a newly developed lateral-flow device. J Clin Microbiol. 2025;63(7):e00226-25.
54. Lander DP, Roland LT. Updates in the Classification of Fungal Sinusitis. Curr Treat Options Allergy. 2023;10(2):93-105.

Sarah A. Ahmed
Department of Microbiology
Faculty of Medicine
Kuwait University
Kuwait

E-mail: sarah.ahmed@ku.edu.kw

Shaoqin Zhou[1,2,3], Richard Kwizera[4], Felix Bongomin[5,6], Louis Okema[7], Jerom Okot[5], Ervin M. Alcanzo[2], Bassey E. Ekeng[8], Yingqian Kang[1], David W. Denning[6], Sybren de Hoog[1,2,3,9], Sarah A. Ahmed[10]

[1] Key Laboratory of Environmental Pollution Monitoring and Disease Control, Ministry of Education of Guizhou, Key Laboratory of Microbiology and Parasitology of Education Department of Guizhou, School of Public Health, School of Basic Medical Science, Guizhou Medical University, Guiyang, China

[2] Department of Medical Microbiology, Radboudumc, Nijmegen, The Netherlands

[3] Radboudumc-CWZ Center of Expertise for Mycology, Radboudumc, Nijmegen, The Netherlands

[4] Department of Research, Infectious Diseases Institute, College of Health Sciences, Makerere University, Kampala, Uganda

[5] Department of Medical Microbiology and Immunology, Faculty of Medicine, Gulu University, Gulu, Uganda

[6] Manchester Fungal Infection Group, School of Biological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, United Kingdom

[7] Division of Otorhinolaryngology, Department of Surgery, Faculty of Medicine, Gulu University, Gulu, Uganda

[8] Department of Medical Microbiology and Parasitology, University of Calabar Teaching Hospital, Calabar, Nigeria

[9] Foundation Atlas of Clinical Fungi, Hilversum, The Netherlands

[10] Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait

Rhinology 64: 3, 301 - 311, 2026

https://doi.org/10.4193/Rhin25.678

Received for publication:

December 4, 2025

Accepted: February 2, 2026

Associate Editor:

Ahmad Sedaghat