Expert Consensus on the Prevention of Secondary Mucormycosis Following Respiratory Viral Infections

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Abstract

The epidemiological patterns of respiratory viruses are complex and highly diverse. Infections caused particularly by SARS-CoV-2 and influenza viruses are frequently followed by secondary mucormycosis, posing significant challenges to clinical management and public health. To address the challenges posed by secondary mucormycosis following respiratory viral infections, the Fungal Prevention and Control Team of the Center for Infectious Diseases at West China Hospital, Sichuan University, convened experts from relevant disciplines across the world, to develop the "*Expert Consensus on the Prevention of Secondary Mucormycosis Following Respiratory Viral Infections"*. This consensus aims to provide systematic guidance and optimize prevention strategies. It identifies high-risk populations for mucormycosis after respiratory viral infections and offers 12 preventive recommendations focusing on four areas: education and training, personal protection, early diagnosis and treatment, and infection control. The document also highlights key measures that remain controversial or insufficiently supported by evidence and outlines directions for future research to promote greater awareness and investigation of mucormycosis.

Key words: Respiratory virus; Mucorales; mucormycosis; SARS-CoV-2; influenza virus; prevention.

1. Background

Fungi of the order Mucorales belong to the kingdom Fungi, phylum Mucoromycota, and subphylum Mucoromycotina. This order comprises of least 11 genera: *Rhizopus*, *Lichtheimia*, *Mucor*, *Rhizomucor*, *Cunninghamella*, *Syncephalastrum*, *Saksenaea*, *Apophysomyces*, *Actinomucor*, *Thamnostylum*, and *Cokeromyces.* Among pathogenic Mucorales fungi, the genus *Rhizopus* is most prevalent, followed by *Rhizomucor*, *Mucor*, *Lichtheimia*, and *Cunninghamella.* These fungi are widely distributed throughout the environment including air, soil, and water, even food. Due to their widespread, they can enter the human body via inhalation, ingestion, or traumatic

inoculation, which leads to mucormycosis. Mucormycosis predominantly occurs in immunocompromised individuals, progresses rapidly, and is associated with high mortality. Global disease burden reports indicate a rising incidence of mucormycosis, with the most pronounced increase in Asia [1]. Due to diagnostic challenges, the true incidence rate is likely to be underestimated [2]. A recent systematic review of 10,335 cases of mucormycosis found 100% mortality rate in untreated patients, while 25.7% mortality among treated patients [3].

Respiratory viruses are a group of pathogens that enter through the respiratory tract, replicate within respiratory mucosal epithelial cells, and cause localized respiratory infections or extrapulmonary complications. This group includes both RNA and DNA viruses spanning at least six viral families [4]: *Orthomyxoviridae* [influenza virus (IV)]; *Paramyxoviridae* [respiratory syncytial virus (RSV), parainfluenza virus (PIV), human metapneumovirus (hMPV)]; *Coronaviridae* [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Middle East respiratory syndrome coronavirus (MERS-CoV)]; *Picornaviridae* [human rhinovirus (HRV), enterovirus (EV)]; *Adenoviridae* [human adenovirus (HAdV)]; and *Parvoviridae* [human bocavirus (HBoV)].

Respiratory viruses worldwide exhibit alternating and overlapping epidemic patterns, with an overall increasing upward trend [5; 6], which not only poses significant challenges for the prevention and control of respiratory viral infections but also increases the risk of secondary complications. Respiratory viral infections, such as SARS-CoV-2, can cause damage to alveolar epithelial cells and trigger the release of pro-inflammatory cytokines and chemokines, resulting in a "cytokine storm" that drives excessive inflammation and immune dysregulation. This immune imbalance and the widespread administration of immunosuppressive agents such as glucocorticoids following viral infection markedly impair host defenses [7]. Additional comorbidities, including diabetes, malignancies, and organ transplantation, further exacerbate this immunocompromised state. Consequently, opportunistic fungi, particularly aggressive members of the order Mucorales, easily invade [8]. In real-world outbreaks, the

aforementioned high-risk factors combined with fragile healthcare systems in resource-limited regions significantly elevate the risk of secondary mucormycosis, that occurs subsequent to a viral infection. For example, during the COVID-19 pandemic, India experienced a sharp surge in mucormycosis cases, placing immense strain on its healthcare infrastructure (https://covid19.who.int/region/searo/country/in; 2023).

In May 2021, the Indian government classified mucormycosis as a notifiable disease. Within just a few months, over 50,000 cases of COVID-19-associated mucormycosis (CAM) were reported, resulting in more than 4,000 deaths [9]. In certain regional hospitals of India, the mortality rate of COVID-19-associated mucormycosis reached as high as 30–50% [9; 10]. During the peak of the pandemic, shortages of critical antifungal agents, including amphotericin B, were reported [11]. Concurrently, the absence of effective community-based risk identification and health management networks substantially impaired control efforts [11]. Beyond India, developing countries including Cambodia, Nepal, Pakistan, and Vietnam have also reported cases of COVID-19-associated mucormycosis [11-13]. Although the number of cases in these regions remains relatively low, they nonetheless highlight an emerging epidemiological trend of mucormycosis amid the pandemic. Literature indicates that affected patients frequently share common risk factors such as diabetes and corticosteroid use, with rapid disease progression and high mortality rates. Numerous studies on COVID-19-associated mucormycosis have been published [14-16], alongside mucormycosis linked to influenza infections [17; 18].

In contrast, reports of secondary mucormycosis following other respiratory viral infections are limited. The reasons remain unclear; it may relate to insufficient pathogen detection, incomplete surveillance data, geographical differences, climate changes, along with changes in the mechanisms and severity of host damage caused by various respiratory viruses. Nevertheless, respiratory viral infections invariably damage the respiratory mucosa, thereby predisposing individuals to invasion by Mucorales. Mucormycosis, in turn, can further exacerbate the pathophysiological progression of

respiratory viral infections and raise mortality among affected patients [19]. Secondary mucormycosis following respiratory viral infections also increases the demand for antifungal agents, and widespread use of these drugs may, in turn, contribute to the emergence of antifungal resistance [20].

Therefore, secondary mucormycosis following respiratory viral infections represents a complex clinical problem and a significant public health challenge, leading to a significant health burden. This issue is particularly alarming in resource-limited countries and regions, where prevention and control are challenging. The established international guidelines offer limited recommendations for managing secondary mucormycosis following respiratory viral infections. Moreover, tailored strategies that address the practical challenges encountered in developing countries still remain absent. The Global Action Fund for Fungal Infections (GAFFI) has emphasized the urgent need for enhanced international collaboration, equitable resource sharing, and the development of standardized preventive measures to improve the global response to fungal diseases (https://gaffi.org/annual-reports/GAFFI annual report 2024).

Developing an internationally applicable expert consensus holds urgent public health significance in this context. This consensus draws on clinical experience and outbreak response practices from experts in countries such as Afghanistan, Cambodia, China, Ethiopia, India, Iran, Malaysia and Pakistan, focusing on high-risk populations for secondary mucormycosis following respiratory viral infections. The aim is to provide healthcare institutions and public health authorities worldwide with systematic and practical strategies for prevention and control. These measures are intended to reduce the burden of severe fungal disease and its impact on public health. To better address the challenges posed by mucormycosis complicating respiratory viral infections, a five-member fungal prevention team from the Center for Infectious Diseases, West China Hospital of Sichuan University, collaborated with domestic and international experts in infectious diseases. Drawing on relevant guidelines and clinical research data [21-24], and following multiple rounds of discussion and revision, they jointly developed the

"*Expert Consensus on the Prevention of Secondary Mucormycosis Following Respiratory Viral Infections*". It should be emphasized that the preventive measures outlined in this consensus are intended specifically for high-risk populations susceptible to mucormycosis following respiratory viral infection and are not applicable to all infected individuals. This distinction reflects the high prevalence and variable severity of respiratory viral infections, ranging from mild symptoms to respiratory failure. Not all affected patients are at risk for secondary mucormycosis or require targeted preventive interventions.

2. Methods for Consensus Development

This consensus was led by the Center for Infectious Diseases at West China Hospital, Sichuan University, in collaboration with 49 multidisciplinary experts from China and additional experts from Afghanistan, Cambodia, Ethiopia, India, Iran, Malaysia and Pakistan. The team comprised key stakeholders from clinical practice (infectious diseases, microbiology), public health (CDC, infection control), and methodology (epidemiology). It focuses on prevention strategies for secondary mucormycosis following respiratory viral infections, integrating the latest evidence-based data with clinical practice experience to develop comprehensive preventive recommendations. It is intended to complement, rather than replace, existing clinical diagnostic or therapeutic guidelines.

(1) Target Population and Intended Users

This consensus targets high-risk populations susceptible to secondary mucormycosis following respiratory viral infections, including individuals with impaired immune function, patients with chronic underlying diseases, those undergoing prolonged immunosuppressive therapy, and critically ill patients in intensive care units (ICUs). It is primarily intended for clinicians in infectious diseases, respiratory medicine, hematology, critical care, emergency medicine, endocrinology, and laboratory medicine, providing standardized preventive strategies and supporting clinical decision-making.

(2) Evidence Retrieval from published literature

The expert panel responsible for developing this consensus researched authoritative medical databases domestically and internationally, including PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang Database. Search terms encompassed "respiratory viral infection," "mucormycosis," "high-risk population," and "prevention strategies," among others. The search covered the inception of each database through February 2025. Emphasis was placed on high-quality studies and expert consensus published within the last five years.

Inclusion criteria comprised clinical studies, guidelines, expert consensus statements, systematic reviews, and meta-analyses related to preventing secondary mucormycosis following respiratory viral infections. Only publications in the Chinese or English language were considered. Exclusion criteria involved duplicate publications, studies of low methodological quality, or literature unrelated to the scope of this consensus.

(3) Methodology for Reaching Expert Consensus

The consensus was developed using a Modified Delphi Method, which was conducted by the drafting team through two rounds of expert consultations.The first round focused on key topics, including identifying high-risk populations, selecting prevention strategies, and recommending antifungal drug use. Experts evaluated each recommendation based on evidence from the literature and clinical experience. For each recommendation, experts rated their agreement using a 5-point Likert scale (1 = strongly agree, 2 = agree with reservation, 3 = undecided, 4 = disagree, 5 = strongly disagree). A rating other than "strongly agree" required explanatory comments and suggestions for refinement. Recommendations that met the pre-defined consensus threshold of ≥80% agreement (combining "strongly agree" and "agree with reservation") were advanced to a subsequent round of revision and discussion. During the second round, the panel specifically reviewed and revised these contentious points. This process ultimately finalized the consensus, resulting in all recommendations being

unanimously approved with a 100% agreement rate and no dissenting or neutral votes. The prioritization of prevention strategies in this consensus reflects the principles of current evidence-based medicine and clinical practice, aiming to ensure both scientific rigor and practical feasibility. Accordingly, the expert panel graded each strategy using the Oxford Centre for Evidence-Based Medicine 2009 Levels of Evidence.

3. Mechanisms of Secondary Mucormycosis Following Respiratory Viral Infections, High-Risk Populations, and Susceptibility Factors

Given the limited reports of mucormycosis co-infection with other respiratory viruses [25], the following discussion is primarily based on studies of secondary mucormycosis following SARS-CoV-2 and influenza virus infections. Following respiratory viral infection, the host immune system undergoes complex alterations that result in immunosuppression or dysregulation, thereby increasing susceptibility to fungal infections such as mucormycosis. In the case of SARS-CoV-2, viral-induced endothelial injury, mediated in part by spike protein interaction with ACE2 receptors, represents an additional pathological step that facilitates fungal angioinvasion. Tissue hypoxia is a critical amplifying factor in mucormycosis pathogenesis. Hypoxia secondary to vascular injury, diabetic ketoacidosis, or severe viral pneumonia impairs phagocyte function, increases iron availability, and promotes fungal angioinvasion, forming a self-reinforcing cycle of ischemia and necrosis [26; 27]. The key mechanisms involved include:

1）*T cell dysfunction and exhaustion*:

Infection with various respiratory viruses can lead to a reduction in both the number and function of T cells. Studies have demonstrated that following SARS-CoV-2 infection, patients experience a significant decline in $CD4^+$ and $CD8^+$ T cell counts, impairing anti-viral immunity and diminishing antifungal defenses [28; 29]. Clinically, severe COVID-19 is frequently accompanied by T-cell dysfunction/exhaustion, which may impair antifungal host defense and thereby increase susceptibility to

mucormycosis [30]. Similarly, influenza virus infection has been shown to inhibit T-cell proliferation and cytotoxic function, which may transiently impair host immune responses [31]; however, clinical evidence directly linking influenza-associated T-cell suppression to an increased risk of mucormycosis remains limited, and reported immune dysfunction in influenza is generally short-lived, this suppression is typically transient, with recovery occurring within approximately two weeks.

2）*Cytokine storm:*

SARS-CoV-2 and influenza virus infections can trigger a cytokine storm [32], characterized by excessive release of inflammatory mediators such as IL-6 and TNF-α. This overwhelming inflammatory response leads to immune dysregulation [33] and may impairs effective antifungal immunity [34]. However, direct clinical evidence linking specific cytokines to mucormycosis remains limited. Elevated levels of inflammatory cytokines may exacerbate systemic inflammation and suppress the activity of antifungal immune cells via negative feedback mechanisms, thereby creating an environment conducive to Mucorales growth [35; 36].

3）*Impairment of macrophage and dendritic cell function:*

SARS-CoV-2 can weaken innate antifungal immunity by directly infecting macrophages and dendritic cells or inhibiting their function [37]. The reduced activity of macrophages may diminish their capacity to phagocytose and kill Mucorales spores, potentially increasing the risk of infection [38]. In influenza patients, macrophage dysfunction is generally transient, with limited long-term effects on susceptibility to mucormycosis.

4）*Reduced B cell and antibody responses*:

SARS-CoV-2 infection may also impair B cell function, leading to decreased production of effective antibodies and further weakening the host's antifungal defenses [39]. Lower antibody levels reduce the host's ability to recognize and clear fungal

316 antigens, thereby increasing the risk of mucormycosis [28]. Clinically, impaired B cell
317 function is closely associated with a higher incidence of mucormycosis in patients
318 undergoing immunosuppressive therapy [40].

319 5）*Neutrophil dysfunction:*

320 Respiratory viral infections can impair neutrophil functions, including phagocytosis
321 and microbial killing. As a critical component of antifungal immunity, neutrophil
322 impairment directly elevates the risk of mucormycosis [41].

323 6）*Disruption of iron metabolism:*

324 Certain respiratory viral infections, particularly SARS-CoV-2 and influenza viruses,
325 can alter host iron metabolism by elevating serum ferritin levels, potentially increasing
326 the bioavailable iron within the host. Iron is a critical nutrient for the growth and
327 pathogenicity of fungi such as Mucorales species. A high-iron environment may
328 facilitate fungal proliferation and dissemination. Studies have shown that iron overload
329 promotes Mucorales growth and can enhance fungal antioxidant defenses, which may
330 contribute to increased virulence and infection severity [42].

331 Based on a comprehensive review of the literature, the high-risk groups for secondary
332 mucormycosis following respiratory viral infections are summarized in Table 1:
333 Table 1. High-risk populations for secondary mucormycosis after respiratory viral
334 infections

Risk Factors	Explanation
Critically ill patients with respiratory viral infections requiring mechanical ventilation	Severe respiratory viral infections can progress to acute respiratory distress syndrome (ARDS), necessitating mechanical ventilation. ARDS is characterized by widespread pulmonary inflammation and exudation, which results in airway damage and increased permeability. These pathological changes compromise the integrity of the normal respiratory barrier, making patients more susceptible to opportunistic mould pathogens. Evidence from critically ill patients indicates that

	mechanical ventilation and invasive airway procedures increase the risk of invasive mould infections [43; 44], including mucormycosis [44]. In addition, improper sterilization or irregular ventilation equipment replacement may be a source of fungal contamination [18].
Immunocompromised patients	
（1）Patients with diabetes mellitus and poor glycemic control	Patients with diabetes often exhibit persistent hyperglycemia, which impairs immune function [45], including reduced neutrophil activity and weakened antimicrobial defenses. A hyperglycemic milieu, particularly in diabetic ketoacidosis, promotes the growth of mucormycetes. Furthermore, diabetes-associated vascular abnormalities and immune cell dysfunction create favorable conditions for the development of mucormycosis [46; 47].
（2）Patients with hematological disorders	Patients with hematologic malignancies such as leukemia and lymphoma, as well as other hematopoietic disorders, often experience profound immune suppression and impaired leukocyte function. Chemotherapeutic agents, immunosuppressive drugs, and bone marrow suppression during treatment further compromise host immunity, particularly neutrophil and other immune cell activity. These patients frequently require prolonged use of immunosuppressive therapies and iron chelators (e.g., deferoxamine), which collectively increase the risk of mucormycosis [48].
（3）Hematopoietic stem cell transplant recipients	Prior to stem cell transplantation, patients typically undergo conditioning regimens involving high-dose chemotherapy and/or radiotherapy, resulting in profound bone marrow suppression and a marked decline in leukocyte counts, particularly neutrophils. Following transplantation, immune system reconstitution requires a prolonged period, and to prevent or manage graft-versus-host disease, patients often receive high-dose immunosuppressive therapy [49-51].
（4）Solid organ transplant recipients	Following solid organ transplantation, patients require long-term immunosuppressive therapy to prevent graft rejection. The procedure is complex and highly invasive, and postoperative management often involves the

	placement of various indwelling catheters, such as urinary catheters and central venous lines, which may further predispose patients to mucormycosis [52].
（5）Other patients receiving immunosuppressive therapy (including those with immune-related diseases)	Beyond patients with hematologic disorders, stem cell transplantation, and organ transplantation, other individuals receiving immunosuppressive therapy also face an elevated risk of mucormycosis. These patients often undergo treatment for autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus, using immunosuppressants like corticosteroids and immunomodulatory agents. Corticosteroids (e.g., dexamethasone) reduce inflammation and limit immune responses against viruses but simultaneously impair antifungal immunity by inhibiting T cell proliferation and function and weakening macrophage antimicrobial activity, thereby increasing susceptibility to mucormycosis. Immunomodulatory drugs, including anti-IL-6 monoclonal antibodies (tocilizumab), cyclosporine, methotrexate, and azathioprine, which suppress immune function, particularly targeting T cells and macrophages, further diminishing host antifungal defenses [53].
（6）Patients with uncontrolled HIV/AIDS infection	When the CD4+ T lymphocyte count falls below 200 cells/μL, the risk of mucormycosis increases significantly. Rhizopus and Mucorales species are the primary causative agents of mucormycosis in HIV-infected individuals. The overall mortality rate of this infection reaches 52.2%, with disseminated cases exhibiting mortality as high as 90% [26; 54; 55].
3. Patients with stage 4–5 chronic kidney disease	Patients with chronic kidney disease often experience impaired immune function, such as neutrophil dysfunction induced by uremic toxins, as well as metabolic disturbances like acidosis. Additionally, frequent invasive medical procedures, including dialysis catheter insertion, collectively contribute to an increased risk of mucormycosis in this population [56; 57].
4. Patients with structural lung diseases, such as bronchiectasis	Patients with cystic fibrosis experience impaired airway clearance due to mucus obstruction, facilitating fungal colonization. In bronchiectasis, mucus plugs and distorted airway architecture create a favorable environment for fungal survival. Similarly, in cavitary lung diseases, the stable conditions within lung cavities (such as oxygen levels, temperature, and humidity) and relatively poor blood supply to surrounding tissues, hinder effective immune cell infiltration [58].

Due to compromised immune function or structural abnormalities of the respiratory tract, the aforementioned populations face a markedly increased risk of secondary mucormycosis following respiratory viral infections. These groups warrant heightened vigilance and targeted preventive measures, as outlined below.

Additionally, several other factors can contribute to an increased risk of secondary mucormycosis following respiratory viral infections; however, these factors alone are often insufficient to classify patients as high-risk. Nevertheless, efforts should be made to minimize or avoid these factors whenever possible. Such risk factors include solid malignancies, chemotherapy, or trauma disrupting normal mucosal barriers, residence in damp environments with fungal exposure, prolonged central oxygen use, extended broad-spectrum antibiotic therapy, and exposure to invasive medical procedures, and severe malnutrition, which has been reported as a contributory factor in gastrointestinal and cutaneous mucormycosis, particularly in resource-limited or debilitated patients (Table 2).

Table 2. Additional Factors Contributing to Increased Risk of Secondary Mucormycosis Following Respiratory Viral Infections

Risk factors	Explanations
Patients with solid malignant tumors, especially those undergoing radiotherapy and chemotherapy	Patients with solid malignant tumors, particularly those receiving chemotherapy and radiotherapy, experience immune suppression due to the treatments. Chemotherapy exerts its anticancer effects by disrupting cellular metabolism but simultaneously impairs immune cell function. During radiotherapy, radiation damages tumor tissues and the surrounding normal immune environment. Additionally, poor nutritional status and reduced immune cell activity in these patients further increase their susceptibility to mucormycosis [26; 40].
Living in damp environments with exposure to fungal contaminants	Mucorales species are widely distributed in soil, organic matter, and dust. Patients residing in damp environments or near soil and organic waste are more likely to be exposed to Mucorales spores. Factors such as mold contamination in household and community settings, poorly maintained air filtration systems in hospitals, fungal contamination in

	operating rooms and intensive care units, as well as mold presence on medical equipment and surrounding environments, all contribute to increased patient exposure to Mucorales spores [39; 59].
Prolonged use of a centralized oxygen supply	Patients receiving prolonged centralized oxygen therapy may face an increased risk of exposure to Mucorales spores if the oxygen supply pipelines are not regularly cleaned and disinfected, as microbial accumulation, including fungal spores, can occur within the tubing.
Prolonged or extensive use of broad-spectrum antibiotics combined with invasive medical procedures	Prolonged or extensive use of antibiotics disrupts the host's normal microbiota, reducing competitive inhibition against fungi such as Mucorales and thereby increasing the risk of infection. Invasive medical procedures, including surgery and catheter insertion, further elevate the chances of Mucorales entering the body through the skin or other routes, especially in immunocompromised patients [60; 61].
Malnutrition / Severe nutritional deficiency	Reported as a common risk factor for gastrointestinal mucormycosis in adults, associated with impaired immune response and poor clinical outcomes [62].

4. Recommended Preventive Strategies

The following recommendations focus on high-risk populations for secondary mucormycosis following respiratory viral infections (Table 1) and outline the necessary measures to be implemented within healthcare settings.

1 Education and Training

Consensus 1: It is recommended that high-risk groups receive comprehensive health education addressing the transmission and impact of respiratory viruses and mucormycosis, along with preventive measures and necessary precautions for both infections (Strong recommendation, Level of Evidence 1a).

Consensus 2: It is advised that educational training on mucormycosis be conducted for healthcare professionals to enhance their ability to recognize and manage the disease in high-risk patients (Strong recommendation, Level of Evidence 1a).

Previous studies on education and training for infection prevention have primarily focused on influenza. Findings indicate that health education targeting influenza can enhance public awareness, promote vaccination uptake, and reduce disease incidence. A systematic review of 21 studies reported that educational interventions, such as oral or combined with written or media training sessions and reminders, significantly improved public knowledge of influenza, promoted preventive behaviors and vaccination rates, and reduced the incidence of influenza [63]. A meta-analysis of randomized controlled trials involving 21,523 participants demonstrated that information- and letter-based educational interventions increased influenza vaccination rates, with even greater effectiveness when combined with improved vaccine accessibility [64]. In addition, another systematic review found that comprehensive health education strategies, such as educational sessions, health prescriptions based on questionnaires, nursing interventions, targeted reminders, and on-site vaccination, were more effective in increasing vaccination rates than traditional notification methods. However, the overall quality of evidence supporting this conclusion was relatively low. These findings suggest that implementing multi-channel, multi-format health education in combination with improved vaccine accessibility can substantially enhance influenza vaccination coverage [65]. Health education provided by general practitioners can also improve vaccination rates for influenza, COVID-19, and pneumococcal vaccines [66]. Another systematic review examined the impact of interventions targeting healthcare workers, including doctors, nurses, and pharmacists, on seasonal influenza vaccination uptake. The results showed that any form of training, education, or reminders provided to healthcare workers significantly increased patients' seasonal influenza vaccination rates compared with no intervention [67].

2 Personal Protection (Vaccination and Respiratory Precautions)

Consensus 3: In the absence of contraindications, vaccination against influenza and COVID-19 is recommended for high-risk populations to lower infection risk and mitigate disease severity (Strong recommendation, Level of

Evidence 2b).

Vaccination effectively prevents influenza and COVID-19, although the protective effects vary with different vaccine types. A 2022 meta-analysis published in The Lancet, which included 220 randomized controlled trials, demonstrated that all vaccines significantly reduced the incidence of influenza across various age groups [68]. High-dose, adjuvanted, and recombinant influenza vaccines are more effective than standard-dose, non-adjuvanted formulations in preventing influenza-related hospitalizations among older adults. However, no significant differences in efficacy have been observed among these three enhanced vaccine types [69]. Another meta-analysis showed that vaccines targeting H1N1 influenza A and influenza B effectively reduce the incidence of influenza and related complications across all age groups. Vaccination against H3N2 influenza A was found to protect children under five years old from infection, though its protective effect was diminished in the elderly population [70]. Another study demonstrated that administering trivalent and quadrivalent influenza vaccines to adults aged 60 and above effectively prevents influenza [71]. A recent systematic review evaluating the effectiveness of globally approved vaccines against COVID-19 infection found that all vaccine types demonstrated effectiveness rates exceeding 50% [72; 73]. Additional research has indicated that influenza vaccination may reduce the incidence of COVID-19 infection in the general population. This effect is possibly due to interferons induced by the influenza vaccine, which possess broad-spectrum anti-viral properties that inhibit viral transmission and replication, thereby providing cross-protection against COVID-19 infection [74]. A study from the Middle East reported that the prognosis of COVID-19 combined with mucormycosis is poor, with mortality rates reaching 66.7% in some cohorts [75]. Therefore, vaccination against influenza and COVID-19, while not directly targeting mucormycosis, may indirectly lower its burden by reducing viral infections that predispose to secondary fungal disease.

Consensus 4: It is recommended that high-risk populations wear masks in public settings to protect the respiratory tract according to the prevention

guidelines for respiratory viral infections in the region and the availability of masks (Strong recommendation, Level of Evidence 1a).

Wearing masks is an effective measure to prevent respiratory viral infections [76]; however, the protective efficacy varies among different types of masks. A study including investigations on the effectiveness of 35 various masks against respiratory viruses such as influenza, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS) found that high compliance with mask-wearing offers better protection. Masks with N95 or equivalent filtration efficiency (e.g., P2) were identified as the most effective in preventing coronavirus infections [77]. However, some reports indicate that, compared to surgical masks, using N95 respirators is not associated with a reduced risk of influenza. Therefore, N95 masks are not recommended for the general public or healthcare workers who are not classified as high-risk [78]. Even in healthcare settings, wearing N95 respirators does not significantly reduce the incidence of respiratory viral infections among healthcare workers compared to wearing medical surgical masks [79; 80]. Taking into account mask accessibility and wearer comfort, it is recommended that high-risk individuals wear masks in public settings, preferably medical surgical masks. When tolerable and available, N95 or equivalent-level masks may also be used.

5. Early Diagnosis and Treatment

Consensus 5: It is recommended that high-risk individuals undergo prompt pathogen testing when respiratory infection is suspected, with priority given to influenza virus and COVID-19, to facilitate early diagnosis and treatment (Strong recommendation, Level of Evidence 1a).

A systematic review including 21 studies compared the impact of rapid molecular diagnostic methods with other approaches (non-rapid molecular diagnostics and antigen testing) for detecting influenza and COVID-19 on clinical outcomes. The results demonstrated that rapid molecular diagnostics shorten testing time and reduce

exposure of uninfected patients, hospitalization rates, length of hospital stay, and unnecessary anti-viral and antibiotic treatments [81]. Another systematic review of randomized clinical trials found that routine rapid respiratory virus testing in suspected acute respiratory infections promoted appropriate influenza antiviral use and reduced unnecessary imaging and blood tests, supported by moderate-quality evidence [82]. A systematic review of rapid multiplex PCR testing for respiratory viruses showed that this method reduced the time to diagnosis by 24 to 22 hours and shortens the hospital stays by 0.82 days. It also improved anti-viral treatment and infection control management for influenza patients [83].

Consensus 6: Early anti-viral treatment is recommended for high-risk individuals diagnosed with respiratory viral infections when effective therapies are available for the identified virus. Additionally, during local influenza seasons, preemptive anti-viral therapy is advised for high-risk patients presenting with influenza-like symptoms prior to obtaining pathogen test results (Strong recommendation, Level of Evidence 1a).

Effective anti-viral treatment can shorten the duration of hospitalization for influenza patients. A 2024 systematic review published in The Lancet, which included eight studies involving 1,424 severe influenza cases, found that treatment with oseltamivir and peramivir reduced hospital stay length for severe seasonal influenza (low-quality evidence), but did not significantly shorten the time to symptom relief (low-quality evidence) [84]. A systematic review and network meta-analysis assessing the efficacy and safety of anti-viral treatments in non-hospitalized COVID-19 patients found that anti-viral therapy significantly reduced the risk of COVID-19-related hospitalization or death (OR = 0.23 [95% CI 0.06–0.96, p = 0.04]). Additionally, the use of anti-viral drugs was not associated with an increased risk of adverse events [85]. An open-label randomized controlled trial involving 3,259 patients with influenza-like illness across 15 European countries found that administering oseltamivir before influenza virus test results were available during peak flu season shortened recovery time. This effect was

particularly notable in elderly patients with severe illness, comorbidities, or prolonged symptom duration, who experienced recovery 2 to 3 days earlier [86].

Consensus 7: It is recommended that tertiary hospitals conduct pathogen testing for mucormycosis in patients with clinical suspicion or unexplained clinical deterioration. Secondary hospitals are advised to either detect the mucormycosis pathogen or establish referral channels for such testing, simultaneously promote the development of regional laboratory networks or hubs to ensure that high-risk patients receive timely and accurate pathogen diagnosis (Strong recommendation, Level of Evidence 5).

Mucormycosis testing is critical for establishing a definitive pathogen diagnosis. Detection methods include direct fungal microscopy, fungal culture and identification, histopathological examination, and molecular techniques such as PCR, metagenomic next-generation sequencing (mNGS), and targeted next-generation sequencing (tNGS). Considering the personnel, equipment, and other resources required for testing, as well as the patient case mix at different facilities, it is recommended that tertiary hospitals possess the capacity for mucormycosis detection. Secondary hospitals should either develop this capability based on their specific circumstances or establish routine referral channels to send specimens for testing.

6. Infection Prevention and Control (Environmental Control, Standard Precautions, and Outbreak Investigation)

Consensus 8: During hospitalization of high-risk individuals, items containing soil, such as fresh flowers and potted plants, should be avoided in patient rooms to reduce exposure to Mucorales spores (Strong recommendation, Level of Evidence 3a).

This recommendation is based on the potential presence of Mucorales in soil [87] and

informed by prior evidence and experience in controlling *Aspergillus* infections [23].

Consensus 9: Wards or rooms housing high-risk patients should be located away from new construction or renovation areas to minimize exposure to mucormycosis spores from airborne dust. If relocation is unavoidable, high-risk patients should be placed in rooms that do not directly face and are as distant as possible from the construction site. Construction areas should implement containment measures, such as barriers and water spraying, to prevent spore dissemination. Other potential sources of aerosolized fungal spores, including agricultural activities, areas with poor ventilation or inadequate HVAC systems, and water-damaged environments, should also be monitored and controlled (Strong recommendation, Level of Evidence 4).

Given the limited research on mucormycosis, the above recommendations are primarily based on evidence and experience from *Aspergillus* prevention and control. One study used questionnaires to investigate the relationship between pre-hospital fungal exposure and invasive fungal disease in 234 immunosuppressed individuals. The survey covered factors such as workplaces and living environments, construction or renovation activities, cleaning frequency, and potted plants. The results indicated that multiple fungal exposures were associated with community-acquired invasive fungal disease in patients with hematologic malignancies [88]. Construction activities within or near healthcare facilities can lead to indoor air contamination with fungal spores, resulting in an increased incidence of fungal infections and, in some cases, nosocomial outbreaks. This risk is particularly heightened when construction occurs near air intake areas [89]. Therefore, when construction occurs within healthcare facilities, a risk assessment should be conducted to evaluate its impact on adjacent areas, such as the same floor or neighboring floors. Sealed physical barriers, such as floor-to-ceiling drywall or plastic partitions, should be installed between construction and non-construction zones. Additional measures include water spraying to minimize dust, designing separate routes to prevent healthcare workers and patients from entering construction areas, and

keeping windows on the side facing the construction site closed when nearby work is underway [90].

Consensus 10: It is recommended that bed linens be collected at the bedside in accordance with fabric management requirements. During collection, placement, or replacement, linens should be handled gently and laid flat to avoid shaking. Linens must be placed in dedicated sealed bags or containers for transport before and after laundering. It is also recommended to use air conditioning filtration systems, indoor humidifiers, and increasing sunlight exposure. In addition, environmental control measures, such as regular maintenance and disinfection of air-conditioning and ventilation (HVAC) systems, and proper handling of other potential fomites including curtains and soft furnishings, should also be implemented to minimize fungal spore dissemination in healthcare settings (Strong recommendation, Level of Evidence 4).

Outbreaks of healthcare-associated mucormycosis can arise through multiple pathways, as various items within the hospital environment may become contaminated and act as vehicles for transmission. Potential sources include bed linens, air-conditioning vents, ambient air, medical equipment surfaces, and even used masks [91]. Therefore, hospital laundry facilities should employ agitation, bleach or other disinfectants, and heat during standard washing, drying, and ironing processes to eliminate microorganisms in linens. Throughout the process of cleaning, packaging, transport, and storage, linens and similar fabric items (e.g., bed sheets) should be protected from contact with environmental contaminants in healthcare. Sterilized bed sheets may be considered for individuals at high risk of mucormycosis [59]. Healthcare facilities should regularly monitor areas potentially contaminated with mucormycosis spores to help reduce and control nosocomial outbreaks.

Mucorales spores have been detected in residential environments, particularly in indoor air, household dust, and damp indoor settings [91]. Studies have shown that indoor spore concentrations are generally lower than outdoor levels; however, enclosed spaces

may expose individuals to higher spore concentrations. Furthermore, limited sunlight exposure and low humidity levels can increase spore counts [92]. Therefore, using air purifiers, heating, ventilation, and air conditioning filtration systems can minimize spore concentrations and reduce exposure to mucormycosis. Employing indoor humidifiers and increasing sunlight exposure may further help limit spore dissemination. The feasibility of these environmental control measures may vary across healthcare settings and regions, and their implementation should be adapted to local resources and infrastructure.

Consensus 11: Standard precautions are recommended for patients with mucormycosis. In a nosocomial outbreak, investigations and control measures should focus on non-sterile products, invasive procedures, environmental sources, and other potential contributors (Strong recommendation, Level of Evidence 4).

Since mucormycosis does not transmit from person to person, standard precautions are sufficient for managing individual infected patients [93; 94]. Existing studies indicate that non-sterile products (such as fabrics, bandages, and probiotic powders), various invasive procedures (including catheter insertions, dental surgeries, and insulin pump use), and environmental sources (air, dust, water, soil) can all contribute to outbreaks of healthcare-associated mucormycosis. Therefore, an investigation and environmental sampling assessment should be considered when a healthcare facility observes an incidence of invasive fungal infections exceeding its baseline or identifies mucormycosis cases occurring more than one week after admission [89; 95]. It should be emphasized that standard precautions apply to patient-level care, whereas prevention of healthcare-associated mucormycosis primarily depends on system- and environment-level control measures.

Additional Recommendations (Consensus 12): Prevention Strategies and Implementation Guidance for Resource-Limited Settings

1. Enhance screening and monitoring of high-risk groups. First, focus on

immunocompromised patients with diabetes, blood cancers, or organ transplants. Regular follow-ups are especially important for patients with COVID-19 to detect early symptoms [96]. Second, develop simple screening procedures. These should combine clinical signs with low-cost tests like direct microscopy for quick initial assessment and identification (Strong recommendation, Level of Evidence 4).

2. Optimize resource allocation by focusing limited resources on critically ill patients, prioritizing access to antifungal medications [97]. At the same time, training for primary healthcare workers to recognize typical symptoms of mucormycosis should be enhanced, thereby reducing misdiagnosis (Strong recommendation, Level of Evidence 4).

3. Strengthening multidisciplinary collaboration through the establishment of teleconsultation networks is recommended. These networks can link resource-limited settings with tertiary hospitals, facilitating remote guidance for diagnosis and treatment [96; 98] (Strong recommendation, Level of Evidence 4).

4. Implement basic infection control measures. Training and enforcement of fundamental respiratory infection prevention practices, such as mask-wearing and hand hygiene, should be strengthened in resource-limited areas to reduce the risk of hospital-acquired infections [99] (Strong recommendation, Level of Evidence 1a). At the same time, public education should be enhanced to promote better diabetes management and hygiene awareness, minimizing exposure to damp and moldy environments and lowering the risk of spore inhalation [100] (Strong recommendation, Level of Evidence 3a).

7. Prevention Strategies Without Established Consensus

Due to limited research, consensus has not yet been reached on certain critical issues. However, these gaps highlight important directions for future investigation.

1 Antifungal Prophylaxis:

Due to limited evidence, no consensus currently exists on preventive antifungal therapy in high-risk individuals following respiratory viral infections that may predispose to secondary mucormycosis. It is recommended to raise awareness of non-pharmacological prevention methods, strengthen monitoring of high-risk populations, and ensure early pathogen testing and imaging for suspected mucormycosis cases to facilitate prompt diagnosis and treatment. For patients with hematologic malignancies, antifungal prophylaxis requires special consideration. The guidelines outlined in the "The Chinese guidelines for the diagnosis and treatment of invasive fungal disease in patients with hematological disorders and cancers (the 6th revision)" [101] **may serve as a reference, but the potential for mucormycosis should also be considered.**

The prevalence of mucormycosis among COVID-19 patients (7 per 1,000) is approximately 50 times higher than the highest recorded baseline mucormycosis rate (0.14 per 1,000) [101]. A meta-analysis including 958 cases of COVID-19-associated mucormycosis, primarily from low- and middle-income countries, reported an overall mortality rate of 38.9% [40]. A multicenter retrospective observational study involving 64 ICU patients with COVID-19 who had undergone solid organ transplantation included 19 patients receiving nebulized amphotericin B for fungal infection prophylaxis. Among those without prophylaxis, 10 patients (22.7%) developed pulmonary fungal infections (9 aspergillosis and one mucormycosis), while only one patient (5.3%) in the prophylaxis group developed an infection. However, survival rates did not differ between the groups. Nebulized amphotericin B may reduce the incidence of pulmonary fungal infections in high-risk populations [102]. A meta-analysis of five randomized controlled trials, including 1,617 patients, evaluated the efficacy and safety of posaconazole for preventing invasive fungal infections in immunocompromised individuals. The results showed that, compared to other antifungal agents, posaconazole prophylaxis was significantly associated with a reduced risk of invasive fungal disease (RR = 0.43, 95% CI 0.28–0.66, p = 0.0001) [103]. However, no research currently addresses whether high-risk individuals require prophylactic antifungal treatment

against mucormycosis following respiratory viral infections. Questions regarding the timing to initiate antifungal therapy and the selection of drug type, dosage, and treatment duration remain unanswered.

2. Immunomodulation:

There is insufficient evidence regarding the effectiveness of immunomodulatory agents in high-risk populations to reduce the risk of mucormycosis. Further research is needed to determine whether these agents should be used and how to select them appropriately.

3. Central Oxygen Supply:

For high-risk individuals requiring respiratory support, it remains unclear whether oxygen delivery systems, excluding ventilators equipped with filters, should incorporate filtration devices to reduce exposure to mucormycosis spores. Further investigation is necessary to address this question.

4. Identification of High-Risk Individuals:

It is recommended that risk assessment and prediction models be developed and implemented to enable early identification of high-risk patients.

5. Risk factors management

Strict metabolic control should be maintained by aggressively controlling blood glucose levels and correcting ketoacidosis. Steroids should be used judiciously, and immunosuppressive therapy should be reversed by discontinuing or reducing immunosuppressive drugs whenever feasible.

8. Future Research Directions

Patients who develop mucormycosis secondary to respiratory viral infections often experience severe illness and high mortality. Future research could focus on the

following areas:

1. There is a significant lack of reliable data on the true incidence and epidemiology of mucormycosis following viral infections, particularly in developing countries where the burden may be systematically underestimated. Most current information comes from single-center reports or case studies, lacking broad coverage and standardized methodology. It is recommended that national or regional surveillance sentinel systems for mucormycosis be established. These systems would enhance case identification and data quality, focusing on monitoring trends of mucormycosis following COVID-19 and severe influenza infections.

2. Vaccine Development: Some fungal vaccines, such as PEV7 and NDV-3A for preventing candidaemia, have already entered clinical trial phases [104]. Future efforts should focus on developing additional effective vaccines for mucormycosis to reduce disease incidence by immunizing high-risk populations. Additionally, as SARS-CoV-2 and influenza viruses evolve, vaccine development is essential to maintain and enhance protective efficacy.

3. Development of Novel Diagnostic Technologies: Given the high incidence of respiratory viral infections, rapid integrated testing for influenza, COVID-19, and other respiratory viruses should be considered. Current diagnostic options for mucormycosis are limited, with no available serological tests. Development of rapid serological assays could enable earlier and faster identification of mucormycosis. Additionally, combined molecular testing kits for respiratory viruses and fungal pathogens could be developed to further reduce diagnostic turnaround times.

4. Early Warning Models: Artificial intelligence and machine learning techniques can be applied to analyze imaging data, microbiome profiles, and host gene expression patterns to develop predictive models for early detection and warning models of mucormycosis.

5. Antimucormycosis Prophylaxis: With further data accumulation, clearer guidelines

can be established regarding indications, timing, and selection of antifungal agents for prophylaxis in high-risk populations.

6. Surveillance and Development of Hospital Infection Control Measures: Establishing a global mucormycosis registry database would facilitate epidemiological comparisons across regions and optimize prevention strategies. Additionally, implementing hospital environmental monitoring systems for Mucorales spores can support the development of dynamic infection control measures.

7. Development of Immunopreventive Strategies: Given the importance of immune defense in mucormycosis pathogenesis and the vulnerability of high-risk populations, further research should explore immunomodulatory therapies. These may include cytokine-based treatments such as granulocyte colony-stimulating factor (G-CSF) and interferon-gamma (IFN-γ); cell-based therapies like adoptive T-cell transfer, CAR T-cell therapy, and monoclonal antibodies; as well as probiotic interventions for prevention and treatment in high-risk groups.

8. Development of Novel Prevention Strategies: In-depth studies on the interactions between mucormycosis pathogens, respiratory viruses, and host cells are needed to elucidate co-infection mechanisms. Insights from such research will support the development of innovative prevention approaches.

9. Limitations of This Consensus

1. Most available studies are retrospective or observational, with few high-quality prospective studies or randomized controlled trials.

2. Although this consensus strictly screened literature sources and integrated expert discussions to form recommendations, some suggestions remain limited by the current lack of robust evidence.

3. The clinical effectiveness of certain recommendations requires further validation

through clinical practice, including multicenter studies and real-world research.

10. Conclusion

Respiratory viral infections are expected to persist globally in the foreseeable future, exhibiting patterns of pathogen alternation and co-circulation. Consequently, the incidence of mucormycosis secondary to these infections is also likely to rise. Mucormycosis will continue to pose a serious threat to patient survival and place a heavy burden on healthcare resources. Ongoing research is essential to clarify the pathogenesis of viral-associated mucormycosis, develop rapid early diagnostic methods, create effective vaccines for immunization, and improve antifungal prophylaxis and novel prevention strategies. These efforts will help reduce disease burden and mortality rates. This consensus provides recommendations based on current evidence; however, given the limited data available for some areas, continual refinement through future clinical practice is necessary.

Funding: This consensus's development and preliminary work were supported by the National Key Research and Development Program of China, Project No. 2023YFC2308800, titled "Research on Pathogen and Epidemic Prevention Systems."

Conflict of interest statement: All experts participating in the development of this consensus affirm that they have no conflicts of interest. This document represents an updated and expanded version of the previously published Chinese consensus. The original Chinese version of the "Expert Consensus on the Prevention of Mucormycosis Secondary to Respiratory Viral Infections" appeared in the West China Medical Journal in March 2025 (West China Med J, 2025, Vol. 40, No. 3).

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