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Review

Survey of current national and international guidance to reduce risk of aspergillosis in hospitals

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SUMMARY

Aspergillus spp. are most commonly associated with disease in the severely immunocompromised host and those with chronic chest disease. The scope of patients at risk is expanding, including intensive care (inclusive of severe viral pneumonia), trauma, burns and major surgery. As exposure or colonization is a prerequisite to *Aspergillus*-related disease, this has prompted a global review of preventative measures recommended in healthcare establishments. This global review includes 75 documents from 24 countries, categorized into clinical, infection prevention and control, and building-related guidance for prevention of invasive aspergillosis (IA). We overview the IA incubation period and different acceptable levels of airborne *Aspergilli* in protected environments (PEs), including critical care and operating rooms. Few documents cover all aspects of prevention, prophylaxis, avoidance, preventative measures and monitoring (environmental and clinical). A multi-disciplinary approach is required to identify and minimize the multiple risks and ensure adequate preventative measures. Most building-related guidance addresses construction and internal hospital alterations, but we also review the importance of good management of the healthcare environment (including ventilation systems) and uncertainties of environmental monitoring. We highlight the differences in standards recommended for protective patient environments including the critical care environment. The large capital investment required for PEs is often limited to patient groups most at risk. Single document comprehensive guidance is lacking, and many countries provide no guidance. Reduction in healthcare-associated acquisition of invasive aspergillosis during vulnerable inpatient episodes requires heightened awareness of patients at risk, careful risk assessment and attentive maintenance of the general hospital environment.

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Introduction

Aspergillus spp. are spore forming, filamentous pathogenic and allergenic fungi, ubiquitous in the environment causing life-threatening disease most frequently in the immunocompromised host, those with chronic obstructive pulmonary disease (COPD) and those in intensive care [1]. A recent global estimate indicated an annual incidence of invasive aspergillosis (IA) of over 2 million, with an 85.2% crude mortality [2]. As many healthcare outbreaks [3,4] have been documented globally, protecting the vulnerable patient from this commonly encountered airborne micro-organism is a challenge. Advances in modern medicine with the use of chemotherapeutic regimens, advanced intensive care, transplantation medicine and immune-modulating agents has resulted in increased patient populations susceptible to this opportunistic infection.

With colonization of the respiratory tract a risk factor for IA [5], the microbiome of the built environment and its interactions with its occupants, particularly healthcare-associated (also referred to as 'nosocomial') acquisition, are important areas of study to minimize individual cases and outbreaks [3,6]. Many outbreaks have been described in haematology [7,8], transplant [9], cardiac surgery [10], neonates [11] and intensive care [12] as well as many postoperative infections [13,14]. Antifungal prophylaxis is often used in those at greatest risk but is impracticable in those at lower risk for long periods, and in acutely ill patients. It is therefore incumbent on healthcare providers to minimize the risks of acquiring life-threatening aspergillosis in hospitals and immediately after discharge.

Within healthcare, many strategies exist to protect the vulnerable patient from infections acquired from the hospital environment. Some evidence supports non-pharmaceutical measures to prevent IA. This includes the use of 'protective environments' (PEs) for the most vulnerable and other measures to avoid environmental exposure. These may be incorporated into clinical pathways, infection control policy, or building design. In this review we (1) summarize and contrast national, continental and global resources and guidelines for protection of patients from aspergillosis in hospitals, with a focus on vulnerable patients and protected environments, and (2) assess some of the evidence base underpinning these guidelines/recommendations to identify key knowledge and practice gaps.

Although acquisition of *Aspergillus* in the susceptible host can occur outside the healthcare environment, this review concentrates on protective measures employed within healthcare facilities and on IA. We have reached out to professional colleagues across the world to access guidelines outside of high-income countries. We include a more detailed review of risks associated with construction sites within healthcare, standards for 'protected' environments and environmental monitoring.

Methods

Search strategy

The published guidelines were obtained, using a combination of: (1) database searches including Medline, Google Scholar and the University of Manchester library resources, using the keywords and phrases, 'aspergillosis', '*Aspergillus*', 'infection prevention', 'guidelines', 'consensus statement', 'healthcare environment', 'healthcare building regulations; (2) accessing global healthcare websites in relation to infection, prevention and control and healthcare building regulations; (3) a request to the GAFFI Ambassador network (https://gaffi.org/who/our-ambassadors/) for country-specific guidelines in relation to prevention of IA; (4) 'snowballing' from acquired documents enabling acquisition of the most sited global guidelines. Some society guidelines are for purchase only and were not obtained. Additional documents including the evidence base for some recommendations are also referenced in this review, but it was not possible to review the entire evidence base for every recommendation here.

Review strategy

We only included guidance documents published from 2000 to 2023 with specific recommendations to protect patients from IA in the healthcare environment. These were then categorized into; (1) clinical guidelines which include management, risk assessment and antifungal chemoprophylaxis; (2) infection, prevention and control (IPC) recommendations; and (3) environmental building regulations and guidelines designed to mitigate environmental airborne risks associated with IA (see Table I). We found some topic cross-over between guidelines; therefore, the categories were assigned according to the most focussed content. Clinical and IPC documents were scored against three categories, 'risks to avoid', 'preventative measures' and 'environmental monitoring', with a total of 18 subcategories of the most discussed topics. Clinical and IPC documents were scored from 1 to 3 dependent on degree of discussion or evidence base and scored 'x' if topic was not discussed.

Building documents were reviewed more specifically in relation to clinical environments included and recommendations for ventilation of protected environments (PEs).

Results

This review includes 75 documents from 24 countries that include recommendations to prevent IA. World Health Organization (WHO) and collaborative continental guidelines are also included, i.e., European, Australasian (Table I). The geographic distribution of documents obtained is shown in Figure 1 which also highlights countries that our correspondents reported as having no specific guidelines or only a local hospital policy. Some documents in languages other than English from a few countries were not obtained, obtainable or translated, but we know from correspondents in those countries that some guidance exists. It is unlikely to cover every aspect analysed here, given the variation we have seen from countries with extensive guidance, but we cannot be sure.

Clinical recommendations for prevention of IA

Some clinical guidance (Table II) provided a general view of *Aspergillus* disease [22,28—30,35—37], while many focussed on more specific aspects of disease such as IA [17,27,29], chronic pulmonary aspergillosis (CPA) [90,91], healthcare-associated pneumonia [32] and respiratory virus-associated IA (VAPA) [19]. Others targeted specific patient groups including adult haematology [15,16,18,20,21,24,25,31], solid organ transplant [26,33], critically ill in intensive care [34], and neonates and children [23,25]. These documents were scored against the same criteria as the IPC documents.

Table I
Summary of guidelines by geographical location and document category included in review

Country/global region	Clinical guidelines		IPC guidelines		Building design guidelines	
	No. of publications included	Reference no.	No. of publications included	Reference no.	No. of publications included	Reference no.
Australia & New Zealand	2	[15,16]	4	[38–41]	5	[70–74]
Belgium	–		1	[42]	–	
Canada	–		3	[43–45]	2	[75,76]
Colombia	1	[17]	1	[46]	–	
Europe (collaborative)	6	[18–23]	–		–	
France	–		4	[47–50]	–	
Germany	1	[24]	2	[51,52]	1	[77]
Greece	1	[25]	–		–	
India	–		1	[53]	2	[78,79]
Ireland	–		2	[54,55]	–	
Italy	1	[26]				
Japan	1	[27]	–		–	
Namibia	1		1	[56]		
Netherlands	–		2	[57]	–	
Saudi Arabia	1	[28]	–		–	
South Africa	–		1	[58]	–	
Spain	1	[29]	1	[59]	–	
UAE	–		–		2	[80,81]
UK	1	[30]	1	[60]	4	[82–85]
USA	7	[31–37]	7	[61–68]	3	[86–88]
Global (WHO)			1	[69]	1	[89]
Total	24		32		20	75
Guidelines exist but not obtained	Brazil, China, Norway, Pakistan, Poland, Switzerland, Tunisia, Russia					
Countries surveyed where no guidelines specific to prevention of *Aspergillus* disease reported	Algeria, Angola, Argentina, Azerbaijan, Chile, Cuba, Democratic Republic of Congo, [a]Denmark, Egypt, Ecuador, Equatorial Guinea, Eswatini, Ethiopia, Gabon, Gambia, Ghana, Guinea, Hungary, Indonesia, Iran, Ivory coast, Kenya, Kuwait, Liberia, Malawi, Malaysia, México, Niger, Nigeria, Oman, Panama, Senegal, South Korea, Togo, Uruguay, Vietnam, Zimbabwe					

[a] Although no individual country guidelines reported, European guidelines apply.

The most common environmental risk factors discussed in the clinical guidance documents were in relation to construction work (12/23) and exclusion of flowers on haematology wards or avoidance of potted plants and soil (8/23). Some alluded to the risks of stagnant water (6/23), with 3/23 mentioning food risk. Food risk was mentioned only in relation to the most immunocompromised risk groups.

In terms of preventative strategies, clinical guidelines tend to focus primarily on pharmaceutical prevention with the use of antifungal prophylaxis, with 8/20 only discussing prophylaxis. Some clinical guidelines focussed on diagnosis and clinical management and did not include prevention and were therefore excluded [86,87], although though some defer to IPC guidance and related papers. Aside from prophylaxis, other common recommendations focussed on the use of PEs for the most immunocompromised (12/23) and use of patient protective masks when transporting patients outside PEs (7/23), especially during periods of building works. Of note, education of staff and patients was more commonly discussed in the more recent publications.

Only 40% of clinical guidelines discussed monitoring for cases of IA, with clinical surveillance being the most common topic (8/23). Only four clinical documents: Khanina *et al.* (Australia) [16], Patterson *et al.* (USA) [35], Ullman *et al.* (Europe) [22] and Fernando *et al.* (Europe) [18] provided a broad overview of preventative measures, with only a cursory mention of non-medical interventions in most documents.

IPC guidance to prevent IA

We identified and sourced 32 IPC guidelines with specific recommendations regarding IA (Table III). IPC guidelines focus more on environmental risks, preventative strategies and monitoring. Overall, the highest scoring and most comprehensive IPC guidelines were Centres for Disease Control (CDC) (USA) [61], Health Protection Surveillance Centre (Ireland) [54], Chang *et al.* (Australia) [38] and Ruiz-Camps *et al.* (Spain) [59]. Education of staff and patients were common themes in IPC documents, contributing to prevention strategies. This included awareness of reduced immunity and increased susceptibility to fungal infection, environmental risks, activities to avoid and other general IPC measures [38,41,45,54,60]. Construction work and dust were the most discussed risk factors (29/32) across all guidelines. Risks associated with water/dampness (24/32) and organic material such as soil, plants and flowers (23/32) were also a common theme.

As observed for clinical documents, PE were the most discussed preventative measure (30/32), however environmental

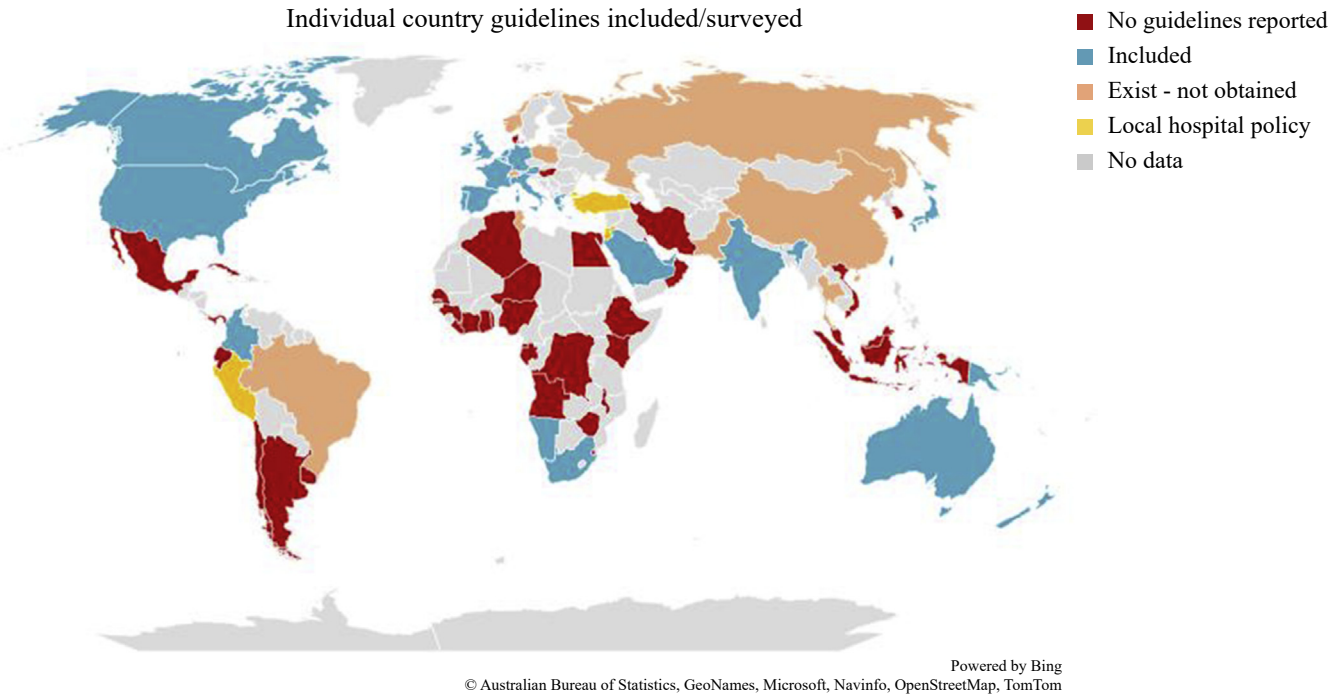

Figure 1. Global distribution of guidelines which discuss the prevention of healthcare-associated invasive aspergillosis or healthcare building design including protective environments.

cleaning (30/32), dust control (29/32) and IA risk assessment (27/32) were main topics for recommendations.

The Centres for Disease Control & Prevention, USA, define a PE as a "specialized patient-care area, usually in a hospital, with a positive airflow relative to the corridor (i.e., air flows from the room to the outside adjacent space). The combination of high-efficiency particulate air (HEPA) filtration, high numbers of air changes per hour (≥12 ACH), and minimal leakage of air into the room creates an environment that can safely accommodate patients who have undergone allogeneic hematopoietic stem cell transplant (HSCT)." However, other definitions and designs exist.

Environmental monitoring was also a main feature of many IPC documents with maintenance of heating, ventilation, and air conditioning (HVAC) systems the most common (27/32). Investigation of outbreaks (25/32), clinical surveillance (22/32) and discussion around environmental air sampling (20/32) were also frequent topics for recommendations.

Building and estates recommendations for IA prevention

Building documents could not be categorized in the same manner as the clinical and IPC guidelines. Building guidelines include room design specifications for isolation rooms, operating theatres and other areas requiring specialist ventilation to reduce microbial load and other air quality parameters in the healthcare environment, e.g., critical care. Maintenance and performance testing of HVAC systems, in particular in specialist areas, are essential quality assurance processes, most often described in IPC-related guidelines.

Table IV lists the building design documents found for this review and highlights categories discussed relevant to control of *Aspergillus spp*. Not all documents refer to *Aspergillus* acquisition risk directly, but many refer to isolation rooms with room differential pressures, air changes and air filter requirements. Not all documents identified could be obtained (and thus were not reviewed) but are listed for reference.

Of the 75 guidelines obtained and reviewed, 40 (54%) overviewed construction work as a significant risk factor for aspergillosis, including 24 IPC documents, six building documents and 10 clinical guidelines. The most discussed topics were dust as a risk factor, a multi-disciplinary approach to planning and risk assessment, environmental sampling, and clinical surveillance. A more comprehensive list of the recommendations to reduce aspergillosis risk from construction work is shown in Table V.

Preventative measures included in some guidance were: sealing off construction sites and clinical areas, i.e., windows, doors, and floor to ceiling barriers; controlling air flow by placing construction sites under negative pressure (and clinical areas under positive pressure); personal protective equipment (PPE) for construction workers; controlling traffic through sites; and enhanced cleaning and control of waste (see Table V).

A PE is also often recommended for the immunocompromised host, and sometimes burned patients, depending on the severity of immunosuppression and availability of isolation facilities. In some documents, this was a general recommendation and in others it was specific to construction. Supplementary Table 1A shows the differences in recommendations for ventilation and design in respect of air change, differential pressures, and filter type for these clinical environments. Although some IPC guidelines have recommendations for hospital environment design, specific parameters for specialist ventilation such as recommended air changes, pressure differentials and filter

requirements are found in healthcare building guidelines. Although these documents do not always refer to IA risk directly, they include room design specifications for isolation rooms, operating theatres and other areas requiring specialist ventilation to reduce microbial load and improve other air quality parameters in those environments.

As the critical care environment is often listed as a high-risk clinical area for IA risk, ventilation design parameters were also reviewed and are summarized in Supplementary Table 1B. As for PE rooms, variation in design is also observed in differential air flow requirements and air changes per hour, with some describing the requirements for a PE room only. In comparison with a dedicated PE room, the air changes per hour (ACH) are generally lower and air filter grade for a critical care environment is generally lower than a HEPA filter.

Environmental testing for *Aspergillus* in the air or on surfaces was recommended in 22 of the published guidelines we reviewed. The indications for testing are shown in Table VI, with monitoring during construction work being the most common. It must be noted that 10/22 of these guidelines do not state an acceptable threshold level for *Aspergillus* spp. (or other fungi). The acceptable range for HEPA-filtered air ranges from $<0.1-1.0$ colony-forming units (cfu)/m^3, and from zero *Aspergillus* to <5 cfu/m^3 in other protected environments (such as intensive care and operating rooms). There is no consensus on acceptable threshold levels for *Aspergillus* spp. for many of the other healthcare environments (Table VII).

Discussion

A recent estimate of the global annual incidence of IA put the total at 2.1 million with about 85% dying [2]. Probably the majority of these cases are community acquired, but this total includes ~500,000 occurring in intensive care and another 27,000 in leukaemia and allogeneic stem cell transplant recipients [2]. *Aspergillus fumigatus*, the predominant pathogen causing IA globally, has been listed in the critical group on the 2022 WHO fungal priority pathogens list [69]. The risk scope of IA is broadening with high-dose corticosteroids, diabetes, underlying chest disease, severe respiratory viral infection, advanced HIV disease, some genetic disorders, liver failure [22,92] and/or other immunosuppressive drugs individually or collectively contributing to risk. The highest risk groups include allogeneic haematopoietic stem cell transplant (HSCT) recipients with graft versus host disease [21], patients undergoing intensive myelosuppressive chemotherapy (e.g., haematological malignancies and some other cancers) [15,18,20,24,93], lung, heart, retransplanted liver recipients [26,33], those taking systemic corticosteroids [1,94,95], premature neonates [23] and medical intensive care patients [92,96,97], including those with severe influenza [98–100], and COVID-19 [94,101,102], severe fever with thrombocytopenia syndrome (SFTS) [103] and recently reported interstitial lung disease [104]. Additional risk groups continue to be included in the expanding scope and definition of *Aspergillus* disease [95,105]. Unanticipated cases of IA can also occur in immunocompetent people as in postoperative aspergillosis [14], ocular infection [106], maxillary sinus [107] open trauma or cases of burns [108]. Any clinical guidance on prevention of IA needs to include a detailed patient risk assessment, and not simply focus on antifungal prophylaxis, which in practice is limited to some haematology patients and lung transplant recipients. Emerging triazole resistance [109–111] is a global concern, reducing the effectiveness of antifungal prophylaxis and treatment efficacy.

The most comprehensive guidance to prevent healthcare-associated IA comes from the developed areas of the globe such as USA, Canada, Australasia and European consortiums. There is no WHO guidance on this topic, even just focussing on operating rooms or high-risk patients. From a global perspective, unified IPC practice is still in its infancy with more recent surveys concentrating on the basics of IPC practice in healthcare [112,113], rather than specialized advice on *Aspergillus*-associated risks. There are a few more generic global guidelines in relation to dampness and moulds in the built environment [89], general mould exposure [114] and general air quality [115].

Guidance specifically related to the risk of healthcare-associated IA is often not included in the more generic IPC guidelines in the UK [116,117] and Europe [118], although typically they do recommend commitment to strategies of healthcare-associated infection prevention and risk assessment or defer to more specific guidelines. Australian [40] and Canadian [45] guidelines do include specific reference to IA risk in their national guidelines.

The primary focus of IPC guidelines is on reducing healthcare-associated or hospital-acquired infection (HAI), either from exposure to other patients with transmissible infection or from organisms in the environment. Patient to patient transmission of *Aspergillus* spp. is rare and only described to occur via exposed infected wounds which can contaminate the surrounding environment [9] or in cystic fibrosis patients [65,119]. Documentation of person-to-person transmission requires molecular typing, whole-genome sequencing or inferred from specific resistance profiles, given how common *Aspergillus* spp. are in the environment and as human lung colonizers.

Environmental control and reduction of exposure are mainstays of preventative measures in healthcare. Their primary focus is therefore on non-pharmaceutical preventative measures, including PEs for the most vulnerable patients, environmental cleaning, control of dust and excess moisture, clinical surveillance and in some scenarios, environmental monitoring. Construction and building works are highlighted by many as a significant risk factor in healthcare, with publication of many associated outbreaks [3,9,93,120]. As a result, many specific guidelines have been written for prevention of this scenario [39,41,50,55,121,122]. Water is another commonly described *Aspergillus spp*. environmental risk factor with outbreaks of IA attributed to contaminated ventilation systems [10,13] water damage (including roof spaces and mouldy ceiling tiles) [61,123] and water-containing medical equipment [11]. With *Aspergillus spp*. found in soil and organic matter, flowers and potted plants are viewed as a risk factor and often are banned from the immediate environment of highly immunocompromised patients. Avoiding gardening activities as an outpatient and avoidance of some foods such as uncooked herbs and spices, soft and blue cheese, and unwashed or unpeeled fruit [18,38,59] are recommended in some guidelines.

Control of dust generated by construction work is one of the most significant preventative measures described with fungal spores contained within the fabric and materials of buildings or accumulating over time in moist spaces [89]. Although vulnerable patients are the highest priority, some guidance includes

Table II
Clinical guidelines scored by aspergillosis risk/prevention/monitoring topic content

Clinical aspergillosis guidelines	Country/Region	Risks to avoid				Preventative measures									Monitoring				
		Construction/works	Avoid flowers/soil	Water (stagnant, damp areas)	Some foods	Antifungal prophylaxis	Protective environment (HEPA)	Masks for transport	Filter on showers	Dust control	Cleaning	Risk assessment	Education staff/patients	*Aspergillus* risk assessment	Environmental air sampling	Clinical surveillance	Outbreak investigation	Monitoring HVAC	Threshold counts
Stevens *et al.* (2000) [36]	USA	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
Walsh *et al.* (2008) [37]	USA	—	—	—	—	3	—	—	—	—	—	—	—	—	—	—	—	—	—
Limper *et al.* (2010) [34]	USA	—	—	—	—	3	1	—	—	—	—	—	—	—	—	—	—	—	—
Grossi *et al.* (2011) [26]	Italy	—	—	—	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—
Al-Abdely *et al.* (2013) [28]	Middle East	—	—	—	—	3	2	—	—	—	—	—	—	—	—	—	—	—	—
Patterson *et al.* (2016) [35]	USA	2	2	2	—	3	1	1	—	—	—	—	—	—	2	2	1	1	—
Kohno *et al.* (2016) [27]	Japan	1	—	—	—	3	2	—	—	1	—	1	—	—	—	1	—	—	—
Ullman *et al.* (2018) [22]	Europe	2	2	2	—	3	2	1	2	—	—	—	—	—	1	—	1	1	—
Tissot *et al.* (2017) [21]	Europe	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
Mellinghoff *et al.* (2018) [24]	Germany	1	—	—	1	3	2	2	—	—	—	—	—	—	—	—	—	—	—
Garcia-Vidal *et al.* (2019) [29]	Spain	—	—	—	—	3	—	—	—	—	—	—	—	—	—	—	—	—	—
Warris *et al.* (2019) [23]	Europe	—	—	—	—	3	—	—	—	—	—	—	—	—	—	—	—	—	—
Maertens *et al.* (2019) [20]	Europe	1	1	—	—	3	1	—	—	—	—	—	—	—	—	—	—	—	—
Husain *et al.* (2019) [33]	USA	1	1	—	—	3	—	1	—	—	—	—	—	—	—	1	—	—	—
Papachristou *et al.* (2019) [25]	Greece	1	1	1	1	3	2	1	1	—	—	—	—	—	1	—	1	—	—
Fine *et al.* (2020) [32]	USA	1	—	—	—	0	1	—	—	—	—	—	—	—	—	—	—	—	—
Koehler *et al.* (2020) [19]	Europe	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
Teh *et al.* (2021) [15]	Australia	—	—	—	—	3	—	—	—	—	—	—	—	—	—	1	—	—	—
Fernando *et al.* (2021) [18]	Europe	2	1	1	2	2	1	1	—	1	1	1	1	1	—	1	—	—	—
Khanina *et al.* (2021) [16]	Australia	2	—	1	—	2	2	1	—	1	1	1	1	2	1	3	2	1	—
Dawdal *et al.* (2021) [31]	USA	2	2	—	—	3	—	—	—	—	—	—	—	—	—	2	—	—	—
Rivas-Pinedo *et al.* (2022) [17]	Colombia	1	—	—	—	3	—	—	—	—	—	—	—	—	—	1	—	—	—
BMJ (2022) [30]	UK	—	1	1	—	3	2	—	—	—	1	—	1	—	—	—	—	—	—
Total references where categories discussed		12	8	6	3	22	12	7	2	3	3	3	3	2	4	8	4	3	0

3: COMPREHENSIVE — thorough, in-depth discussion with strong recommendations or strong evidence base, 2: MODERATE — some discussion or limited evidence base, 1: MINOR — superficial mention, defers to separate guideline, or only general not specific to *Aspergillus* prevention. —, not classified.

measures to protect immunocompetent individuals such as construction workers. Environmental risk assessment is specifically recommended prior to any on-site building works [122]. These assessments require clinical knowledge of susceptible populations, local estate, and national building standards. Multi-disciplinary teams are therefore commonly advised for investigations into HAI outbreaks or planning and building design (see Table V).

In building and IPC guidance where IA (or invasive mould infection) risk assessment is described, patient groups are classified in up to four categories by degree of immunosuppression or department location. The patient risk category is linked to the dust risk likely generated according to construction activity. These are often presented as a risk matrix. Standard precautions apply with additional measures suggested by increasing risk score category. Relocating vulnerable patients away from any remediation or construction area is often recommended. The use of masks by patients outside PEs is often recommended (Table V), however their benefit is debatable, and masks probably vary in efficiency for this purpose [61,124].

HEPA-filtered positive pressure PE isolation facilities are usually designed specifically for the severely immunocompromised. However, there remains controversy around their efficacy and the link between environmental exposures levels and infection [46,125—128]. Some guidance only suggests HSCT patients be housed in PE [61,67], yet others suggest expanding the scope to other vulnerable patients [35,129,130], including (for example) burns patients [1,130]. This observed variation in scope of use and design (see Supplementary Table 1A), adds further to the controversy around efficacy.

Other positive pressure environments, such as critical care units, may be designed with lower grade air filters to HEPA filtration [85]. These environments can still be protective in

Table III
Infection prevention and control guidelines scored by *Aspergillus* risk/prevention/monitoring topic content

Infection control guidance	Country	Risks to avoid				Preventative measures									Monitoring				
		Construction & dust	Water	Avoid flowers/soil	Certain foods	Protective environment	Cleaning environment	Dust control	*Aspergillus* risk assessment	Masks for transport	Education for patients/staff	Control of moisture/leaks	Antifungal prophylaxis	Filter on showers	Maintenance of HVAC	Investigation of outbreak source	Clinical *Aspergillus* surveillance	Environmental air sampling	Threshold counts
Health Canada (2001) [44]	Canada	3	3	2	—	1	3	3	3	2	2	1	—	—	3	1	1	—	—
Gangneux (2002) [47]	France	1	—	1	1	1	2	1	3	—	—	—	1	—	3	1	1	3	2
CDC (2003a) [61]	USA	3	3	3	1	3	3	3	3	2	3	3	—	—	3	3	3	3	2
CDC (2003b) [62]	USA	3	3	3	1	3	3	3	3	2	3	3	3	—	3	3	3	2	—
Loddon Mallae (2003) [39]	Australia	3	3	1	—	3	3	3	3	2	3	3	—	—	1	1	—	3	2
Warris (2005) [57]	Netherlands	3	3	1	1	3	3	1	3	—	—	1	3	1	—	1	—	—	—
Siegel *et al.* (2007) [66]	USA	3	1	2	1	3	3	3	3	3	1	1	1	—	3	1	1	—	—
CDC (2008) [63]	USA	—	—	—	—	—	3	—	—	—	—	—	—	—	—	—	—	—	—
Yokoe *et al.* (2009) [68]	USA	3	3	3	—	3	3	3	3	3	—	3	1	—	3	2	2	2	—
Weber *et al.* (2009) [67]	USA	3	3	3	1	3	1	3	3	1	3	3	1	—	3	3	3	2	1
CCDIC (2010) [43]	Canada	3	2	2	1	3	3	3	1	2	1	2	2	—	3	2	2	—	—
Robert Koch Institute (RKI) (2010) [52]	Germany	3	1	2	1	3	2	2	1	2	1	1	1	—	1	1	2	1	2
Ruiz-Camps *et al.* (2011) [59]	Spain	3	2	2	2	3	3	3	3	1	2	2	3	1	1	2	2	3	3
SF2H-SFMM (2011) [50]	France	3	1	1	1	3	2	3	3	1	1	1	2	—	1	3	2	3	3
Gangneux *et al.* (2012) [48]	France	3	—	—	—	3	3	3	3	1	1	—	—	—	1	3	1	3	3
Me'heust *et al.* (2013) [49]	France	1	3	1	1	2	1	1	3	—	—	1	—	—	—	1	1	3	1
Conseil Supérieur de la Santé 8580 (2013) [42]	Belgium	3	1	—	—	3	2	2	1	1	—	1	—	—	3	—	—	—	—
Saiman *et al.* (2014) [65]	USA	3	3	2	1	2	2	3	1	1	2	3	—	—	2	—	1	—	—
Chang *et al.* (2014) [38]	Australia	3	2	1	3	2	3	3	3	3	2	2	2	—	3	3	1	3	2
Northern Territories (2015) [41]	Australia	3	1	1	—	1	3	3	3	2	3	1	1	—	1	2	—	3	3
PHS Scotland (2016) [60]	Scotland	3	1	1	—	3	2	2	3	2	3	2	1	—	2	3	1	3	2
IPAC Canada (2016) [45]	Canada	3	—	—	—	1	3	3	3	—	2	—	—	—	3	3	1	—	—
HPSC (2018) [54]	Ireland	3	2	1	—	3	3	3	3	1	3	—	3	—	3	3	2	3	3
NHMRC (2019) [40]	Australia	3	1	1	—	3	3	3	3	1	1	—	—	1	1	1	—	1	—
Alvarez-Moerno & Combrazia (2019) [46]	Colombia	3	1	—	—	3	3	3	3	2	1	1	3	—	1	3	2	3	—
Talento (2019) [55]	Ireland	3	1	1	—	3	3	3	3	2	2	—	3	—	1	2	2	2	2
Saran *et al.* (2020) [53]	India	1	3	—	—	3	—	2	—	—	—	2	—	—	3	1	—	1	1
CDC (2020) [64]	USA	3	3	1	—	3	3	3	3	—	—	3	—	—	3	3	—	1	—
Dept of Health: Republic of South Africa (2020) [58]	South Africa	—	—	—	—	1	3	—	—	—	—	—	—	—	—	—	—	—	—
WHO (2022) [69]	Global	—	—	—	—	—	—	—	—	—	1	—	1	—	—	—	3	—	—
KRINKO (2022) [51]	Germany	3	—	1	1	3	2	2	2	2	—	—	1	—	2	—	2	—	—
Namibia Ministry of health [56]	Namibia	1	—	—	—	1	1	1	—	—	1	—	—	—	1	—	—	—	—
Total references where categories discussed		29	24	23	14	30	30	29	27	22	21	21	18	3	27	25	22	20	15

3: COMPREHENSIVE — thorough, in-depth discussion with strong recommendations or strong evidence base, 2: MODERATE — some discussion or limited evidence base, 1: MINOR — superficial mention, defers to separate guideline, or only general not specific to *Aspergillus* prevention. —, not classified; CCDIC, Centre for Communicable Diseases and Infection Control; CDC, Centres for Disease Control; HPSC, Health Protection Scotland; HVAC, heating, ventilation, and air conditioning; KRINKO, Commission for Hospital Hygiene and Infection Control; NHMRC, National Health and Medical Research Council.

Table IV
Building and design documents for hospital environments by resource

Building and design guidelines	Country	Year	For purchase	Hospital environments													
				Isolation rooms	AII * (negative pressure rooms)	Protective environment (positive pressure ± HEPA)	PPVL	Operating theatres	Critical care	Air changes	Differential pressure	Portable HEPA filters	Monitoring HVAC	Aspergillus risk assessment	Environmental air sampling	Construction
WHO (2009) [89]	Global	2009										x			x	
Health Building Note (HBN) 04-01 [82]	UK	2009		x	x		x						x			
NHS England Health Building Note HBN 00-09 [83]	UK	2013		x										x	x	x
NHS England Heath Building Note 04-02 [84]	UK	2013		x			x		x	x	x					
Kulpman *et al.* (2016) (DGKH) [77]	Germany	2016			x	x		x	x		x		x			
ASHE [86]	USA	2018		x		x		x		x		x		x		x
DHA Health Facility Guidelines 2019 Part D [80]	UAE	2019								x						
DHA Health Facility Guidelines 2019 Part E [81]	UAE	2019		x	x	x					x	x		x	x	
AHFG Part D [71]	Australia	2020		x	x	x							x	x	x	x
Rungta *et al.* (2020) [78]	India	2020			x	x			x	x	x		x			
Health technical guideline HTG-2020-004 [73]	Australia	2020		x	x	x	x	x		x	x		x			
Health Technical Advice HTA-2020-004 [74]	Australia	2020		x	x											
NHS England. Health Technical Memorandum 03-01 [85]	UK	2021		x	x	x	x	x	x	x	x		x			
Zia *et al.* (2021) [79]	India	2021										x				
NSW Engineering Services Guidelines GL. 2021 014 [72]	Australia	2021		x	x	x		x	x			x				
Australian Standard AS1668.2-2012 [70]	Australia	2012	ǂ													
CAN/CSA Z8000-18. Canadian Health Care Facilities [75]	Canada	2018	ǂ													
CAN/CSA Z317.2-19 [76]	Canada	2019	ǂ													
ANSI/ASHRAE/ASHE Standard 170-2021[87]	USA	2021	ǂ													
Facility Guidelines Institute [88]	USA	2022	ǂ													

x indicates topic included; ǂ not purchased for review, included for reference; * AII = 'airborne infection isolation' rooms, not relevant to invasive aspergillosis but category may be of value to some readers. AHFG, Australian Health Facility Guidelines; ASHE, American Society of Healthcare Engineers; DHA, Dubai Healthy Authority; HEPA, high-efficiency particulate air; HVAC, heating, ventilation, and air conditioning; NHS, National Health Service; NSW, New South Wales; PPVL, positive pressure ventilated lobbies.

reducing the microbial load of air with directional air flow and a higher number of air changes per hour [131] than a standard ward. Patients in critical care often have risk factors for IA [100,132]. Some guidance, but not all, includes critical care as a high-risk category in *Aspergillus* environmental risk assessments [39,46,54,59,71]. Uncertainty surrounds the timing of airway acquisition of aspergillosis, with suggestion of early invasion in influenza (i.e., on admission to the intensive care unit, thus probably community acquired) and later in COVID-19 (i.e., at seven to 10 days after intensive care unit admission, thus possibly healthcare-associated [133]). Some studies have observed varying levels of *Aspergillus* spp. in critical care environments [12,134], which may in part be due to the variations in design shown in Supplementary Table 1B.

The COVID-19 pandemic highlighted the importance of indoor ventilation, with an initial demand for source control negative pressure environments. Some observed increase in COVID-19-associated IA (CAPA) were associated with conversion of critical care areas to negative pressure environments, thus removing the protective element to the patient [101].

Standard operating theatres, although not HEPA-filtered, also reduce microbial load via a high number of air changes per hour [85,135]. Theatres with ultra clean ventilation (UCV) systems, which utilize laminar air flow (LAF) systems using high rates of HEPA-filtered unidirectional air [61], can provide enhanced protection, for example, in orthopaedic surgeries [136]. These LAF systems may control IA outbreaks in severely immunocompromised patient populations [7]. However, due to high costs and lack of data describing survival benefit, these systems are not recommended for the general hospital ward setting [61].

Any specialist hospital ventilation system comes at a cost. It requires separate air handling units and expensive filters, regular maintenance, replacement of filters and revalidation [54]. Maintenance and performance testing of these ventilation systems are recommended as essential quality assurance processes in almost all guidance documents, further adding to cost and complexity.

In establishments with no isolation facilities, the use of portable HEPA filter devices has been suggested as an alternative to protect vulnerable patients [79,137], most often in relation to protection during construction activities. More recently, similar devices have been suggested to reduce the air bioburden in response to the COVID-19 pandemic, using a range of technologies [138—142].

Most preventative measures for water outlets are recommended to reduce *Legionella* spp. exposure. These same recommendations could also reduce *Aspergillus* spp. exposure, such as filters on showers [22,25,40,56,59].

Clinical and/or laboratory surveillance is often recommended for IA high-risk groups [19,31,35,46,54,55,61,67,68], particularly during on-site/nearby construction work. Screening for community-acquired colonization prior to induction of neutropenia in haematology patients can aid clinical decisions with the use of prophylaxis or early treatment of infection but may not be relevant in other patient groups (e.g., critical care patients).

Table V
Construction-related risk reduction strategies by reference

Construction-related infection prevention strategy	References	*Total*
Dust as risk factor/dust control	[16,18,27,38–44,46–50,54,55,57,59–62,64–68,71,81,83,85,86]	32
Aspergillus risk assessment recommended	[16,38–44,46,47,50,51,54,55,59–62,64,66–68,71,73,81,86]	26
Multi-disciplinary team approach to risk assessment/ planning	[16,18,25,38–44,46–48,50,51,54,55,59,61,66–68,71,83,85,86]	26
Dust barriers (floor to ceiling)/seal off clinical areas (windows/doors)	[16,38–44,46–48,50,51,54,55,60–62,64,67,68,71,83,86]	24
Environmental air sampling discussed	[16,22,25,35,38,39,41,46–50,54,55,59–62,67,68,71,81,83]	23
Adjacent spaces under positive pressure (work area negative pressure)	[16,18,38–44,46,50,54,55,59,61,62,64,67,68,71,81,83,85]	23
Clinical surveillance recommended	[16,18,27,31,35,38,43,44,46–51,54,55,60–62,66–68]	22
Protective environment (HEPA) for high risk/susceptible	[16,20,22,24,25,27,35,38,41,43,46,48,50,51,54,59–62,67,68]	21
Regular/enhanced cleaning of areas adjacent to construction or high-risk areas	[16,38–44,47,49–51,54,55,59,61,62,67,68,71,73]	21
Dust extraction with HEPA vacuum	[16,38–44,51,54,55,59–62,67,68,71,73,81]	20
FFP3/fluid resistant masks for high-risk patients outside protective environment	[16,18,24,33,38,39,41,43,46,50,51,54,59–62,66–68]	19
Identify high-risk patients/classification/relocate or segregate at-risk patients	[22,32,35,38,39,41,43,44,46,50,51,55,59,61,64,67,68,86]	18
Traffic control – limit traffic through construction site/ controlled entrance/exit	[38–44,50,54,59,61,62,64,67,68,71,81,86]	18
Education for patients/staff	[16,18,38–41,43,46,50,51,54,55,59,61,62,65,67]	17
Contain waste disposal	[38–42,44,47,51,54,55,59,61,62,71,83,86]	16
Review ventilation/filters, to high-risk areas	[16,18,38,39,41,50,54,55,59–62,64,67,68,83]	16
Wet mop areas to control dust	[39–42,44,50,51,54,59–62,67,71,83]	15
Risk matrix	[38,39,41,42,46,50,54,55,59,61,71,83,85,86]	14
Dust mats for construction workers outside construction site	[39–42,44,50,54,59–61,67,68,71,83]	14
Antifungal prophylaxis for high-risk group recommended	[16,18,27,41,46,50,51,54,55]	9
PPE for construction workers	[39,41,42,44,50,54,55,59,61]	9
Provide threshold counts for environmental air monitoring	[39,41,47,48,54,55,59,60]	8
Replace ceiling tiles for inspection	[39,41,42,44,54,67,71,73]	8
Monitoring checklist	[16,38,39,41,46,50,64,83]	8
Periodically review micro/histological/post-mortem data	[43,50,54,55,59,61,67]	7
Reporting breaches	[40–42,54,61,64,81]	7
Holes repaired <8 h	[39,41,42,59,83]	5

HEPA, high-efficiency particulate air; PPE, personal protective equipment.

A key consideration in management of outbreaks and determining whether an observed case of IA is hospital- or community-acquired, is the incubation period. Diagnosis of IA can be difficult and determination of the first day of infection is often impossible as early clinical and radiological features are absent. Clinical studies vary in observed incubation period, from 48 h] in trauma- and burn-related IA [1], one to five days with IA complicating severe influenza [100],15 days after onset of aplasia in acute myeloid leukaemia [143], 42 days post-transplant in cystic fibrosis [144], from 13 to 97 days after allogeneic stem cell transplantation [145], and many months in a colonized heart transplant recipient [1] and COPD patients [146]. Estimations of *Aspergillus* incubation periods in outbreak investigations are therefore often not defined [21,147] or described as unknown [38,57,61]. Airway or nasal colonization (at least partly linked to patient genetic variants) prior to hospitalization probably impact on attack rates and could alter incubation period [145,148,149].

Definitions have been proposed for hospital-acquired IA ranging from one to 10 days from hospital admission (24 h [150], seven days [129],10 days [93,151,152], often with a caveat of no evidence of infection prior to admission. As there is no consensus

Table VI
Indications for environmental testing according to reference

Indication for environmental testing/reference	Number (percentage)
Monitoring during construction [16,38,39,41,46–48,50,54,55,60,61,81]	13/22 (59%)
Outbreak investigation [16,25,35,38,39,48,50,54,59,67,68]	11/22 (50%)
Commissioning of theatres/protective environments [16,38,39,41,54,59–61,71,81,83]	11/22 (50%)
To check efficiency of filters [22,25,53,59,61]	5/22 (23%)

Table VII
Environmental *Aspergillus* spp. threshold values in cfu/m^3 according to country reference

Country	Citation	HEPA	High risk	Protected Environment	Unprotected Environment	Not at-risk population
		(cfu/m^3)	(cfu/m^3)	(cfu/m^3)	(cfu/m^3)	(cfu/m^3)
Australia	Loddon Mallae Region (2003) [39]	<0.1	<1			<100 & <4
	Chang *et al.* (2014) [38]	<0.1		<5	15	
	Northern Territories (2015) [41]	<0.1		<1		<4
Europe	Ullman *et al.* (2018) [22]				>25	
	Gangneux (2002) [47]			<2 (<5 other fungi)		
France	SF2H-SFMM (2011) [50]			no *Aspergillus*	≤2	
	Gangneux *et al.* (2012) [48]			<2 air (and per 25 cm surface)		
UK	HPS Scotland (2016) [60]	<0.1	<5			
Ireland	HPSC (2018) [54]	<1			<5	
	Talento (2019) [55]	<1			<5	
Spain	Ruiz-Camps *et al.* (2011) [59]			0.5	>25	
India	Saran *et al.* (2020) [53]	<0.1				
Guidelines where environmental testing suggested but thresholds not stated: [16,25,35,46,58,61,67,71,81,83]						

cfu/m^3, colony forming units per cubic metre; HPS, Health Protection Scotland; HPSC, Health Protection Surveillance Centre.

on the definition of HAIs [16,35,61,67,147], clinical surveillance is recommended in high-risk patients or during high-risk events such as construction [48,152,153] and when high-quality antifungal prophylaxis is not given. What precisely this consists of in different clinical settings varies considerably, and its cost-effectiveness has been questioned. All cases should prompt investigations into potential environmental sources [16,39,58].

Although 22 published guidelines in this review (Table VI), suggest environmental testing has value in some instances, 10/22 of these guidelines do not state an acceptable threshold level for *Aspergillus* spp. (or other fungi). The scope of environmental testing methodology is broad, encompassing passive [154] and active air monitoring [155—157], surface sampling [158,159] and particle counting [61,41,71,160]. The fundamental problems associated with assessing air contamination have been described by many [49,61,161]. Variation in methodology including equipment used, culture media incubation temperature or particle size measured [157,160—162] also add to uncertain accuracy and comparability of results. Differences in units of measure also apply to the methodology used. Air samplers extract a measured volume of air and are therefore measured in cfu/m^3. Settle plates rely on gravity and fallout of viable spores in the air falling on to an agar surface over time. These units are measured as cfu/d(m)^2/time [156,158]. Surface sampling uses a defined surface area for measurement [154,158]. Some suggest a combination of methods is more likely to provide a better overall picture [155,157,161].

Regardless of methodology used, environmental testing as an infection control measure is still a contentious issue as many suggest a lack of evidence and correlation of infection and environmental levels of *Aspergillus* [59,61,62,67,163]. This may in part be due to the lack of standardized methodology, and rarity of these infections which may present a long time after exposure, making them difficult to prove with standard statistical methods. However, other accounts demonstrate high levels correlated with new cases [10] and preventative measures reduce levels of infection [120,125,128,155]. Molecular typing methods have shown benefit in outbreak and epidemiological studies [12,153,164—166] including investigation of azole-resistant strains [167].

Outdoor levels of fungi vary by geographical location and season [168,169]. Total indoor fungi can range from 10^1 to 10^3 cfu/m^3 [170], with contaminated air spaces reaching much higher levels. The threshold levels suggested in healthcare vary as can be seen in Table VII, although it must be noted that these thresholds are for active air sampling only and measures are in cfu/m^3. The difficulty in interpretation lies in the likely differences in susceptibility in clinical risk categories and protected environments (i.e., HEPA-filtered environment, protected, and unprotected hospital locations). The WHO [89] recommend control of moisture within buildings rather than setting acceptable indoor fungal levels.

The guidance for HEPA-filtered rooms is reasonably straightforward as HEPA filters clear 99.9% of organisms, therefore a range of 0.1 to <1 cfu/m^3 is deemed acceptable. There are also recommendations for operating theatres [85,135]. However, in other PEs such as intensive care units, which are not necessarily HEPA-filtered but (should) have a higher standard of air filtration compared with a standard ward, there is an absence of specific thresholds for these areas. In 2016, reclassification of filter types according to efficiency against a range of particle sizes [171] prevents direct comparison, with many guidelines published prior to this change. The variation in the scope, definition, and design of protected environments also contributes to the application of such thresholds.

Rather than specific thresholds, some suggest establishment of baseline levels [46,54,55,81] with the Health Protection Surveillance Centre (HPSC) recommending weekly testing for four weeks prior to construction projects [54]. In this instance, rising environmental levels would prompt investigation into breaches of environmental controls and further risk assessment.

A summary of the key points raised in this review is shown in Table VIII.

To enable further understanding and therefore implementation of suitable preventative strategies, more studies are

Table VIII
Protecting patients from aspergillosis in hospital - Summary of key points

General
• Few guidelines are comprehensive and include recommendations on clinical factors, IPC recommendations and building design
• IA risk does vary between establishments, individual locations in healthcare environments, by patient populations and by individual patients within those populations.
• Development of preventative measure requires a multi-disciplinary approach to risk assessment considering both patient and environmental risk/building design
Clinical challenges
• Expanding scope of susceptible hosts, including temporary risk factors such as respiratory viral infection and corticosteroid therapy
• Early and accurate diagnosis of IA
• Documentation of antifungal resistance, with a low sensitivity of culture and slow results
• Lack of correlation with environmental levels of *Aspergillus spp*. and clinical disease
• Large variation in incubation periods for IA in different patient groups
• Frequent low-level human lung colonization and temporal cross-over of exposure from the community and healthcare facilities
• Unknown extent of antifungal resistance in hospital environment
IPC challenges
• Lack of a definitive (evidence-based) definition for community vs healthcare-associated IA
• No consensus on acceptable threshold levels for *Aspergillus* in non-HEPA filtered environments
• Lack of consensus for when and how frequently environmental testing should be performed in healthcare settings
• Lack of consensus for standard method for environmental testing (air vs surface vs continuous monitoring) and how to establish a baseline or assess when an acceptable level is breached
• Variation in design and specifications of protective environments

HEPA, high-efficiency particulate air; IA, invasive aspergillosis; IPC, infection prevention and control.

required to understand the relationship between the environmental microbiome and association with clinical disease, particularly with respect to the critical care environment and immune competent host.

Author contributions
S.B. and D.D.: Conceptualization, Methodology. S.B.: Data curation, Visualization, Investigation, Writing — Original Draft Preparation. S.B., D.H. and D.D.: Validation, Formal Analysis, Resources, Writing — Reviewing and Editing. D.D.: Supervision.

Conflict of interest statement
The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

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