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General review

A systematic review of epidemiology, risk factors, diagnosis, antifungal resistance, and management of invasive aspergillosis in Africa

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ABSTRACT

Invasive aspergillosis (IA) affects more than 300,000 people annually worldwide with a case fatality rate reaching 80%. However, in Africa despite the presence of risk factors for the development of IA, the burden of these fungal infections remained unknown. This systematic review aimed to update the available information on the epidemiology and the therapeutic management of IA in Africa. The published papers were systematically searched on major medical databases from September 20 to October 10, 2021. The list of references of eligible articles and the Google scholar database were also checked in order to search for possible eligible articles. Results were reported following the Preferred Reporting Items for Systematic and Meta-analyses (PRISMA) guidelines. The search yielded 1864 articles of which 29 met the inclusion criteria. This systematic review showed the existence of IA in Africa. The prevalence of IA can reach 27% with a fatality rate of more than 60%. The most common clinical form of IA found was invasive pulmonary aspergillosis. The main predisposing conditions identified were neutropenia, HIV/AIDS, renal transplant recipients, and renal failure. *Aspergillus* section *Flavi* and *Nigri* were the main *Aspergillus* species identified and *Aspergillus* section *Fumigati* was uncommon. The main management strategy for IA cases was to start antifungal therapy only after a failure of broad-spectrum antibiotic therapy. This review provided evidence of the existence of invasive aspergillosis in Africa and especially a high rate of undiagnosed invasive aspergillosis cases.

1. Background

Aspergillus spp. are saprophytic fungi found in soil and decomposing vegetable materials. These species are also capable, particularly in case of immunodepression of causing potentially fatal aspergillosis [1]. Indeed, these fungal agents are responsible for more than 300,000 cases of invasive aspergillosis (IA) annually worldwide [2]. Invasive aspergillosis covers a wide spectrum of clinical diseases including invasive pulmonary aspergillosis, invasive sinus aspergillosis, central nervous system aspergillosis, and disseminated aspergillosis [3]. The increase of IA cases is correlated with the increase of patients with risk factors such as patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) and intensive chemotherapy [3]. In addition to these traditional risk factors, non-traditional risk factors including intensive care unit (ICU) patients, post-operative patients, patients with chronic pulmonary diseases, patients with acquired immunodeficiency syndrome (AIDS), patients undergoing immunomodulatory treatment [4], patients with influenza infection [5], and patients with coronavirus disease (COVID-19) [6] have emerged worldwide. Despite the recent advances in diagnosis and treatment, the lethality rate associated with invasive aspergillosis still ranges from 30 to 80% [1]. Some studies showed a reduced survival rate when the infection is induced by *Aspergillus* with high minimum inhibitory concentrations (MIC) for azole antifungals [7]. The identification of patients with predictive factors of mortality associated with an early biological diagnosis and the administration of an effective systematic antifungal treatment lead to better clinical outcomes of invasive aspergillosis [8]. However, the absence of specific clinical signs of invasive aspergillosis hampers the early

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microbiological diagnosis of this fungal infection. This situation is even more worrying in countries with limited resources. In fact, in these countries, in addition to low performance of health system, there is a lack of qualified personnel in medical mycology and a low awareness of medical personnel on the burden of invasive fungal infections. This low awareness could lead to under-diagnosis and mismanagement of IA with the consequence of increased fatality rate. This could also increase the selective pressure on antibiotic resistance genes due to the abusive use in these countries of antibiotics in cases of infectious diseases. The present systematic review aimed to update the available information on the epidemiology and therapeutic management of IA in Africa.

2. Methods

2.1. Data sources and search strategy

This systematic review is registered on PROSPERO (CRD42021279208). We systematically searched for articles on major medical databases namely PubMed, African Journal OnLine (AJOL), ScienceDirect, and Cochrane library. The search covered the period of September 20 to October 10, 2021. Results were reported following the Preferred Reporting Items for Systematic and Meta-analyses (PRISMA) guidelines [9]. A search strategy was developed based on the epidemiology and management of invasive aspergillosis in Africa. Electronic search on the selected databases was performed with the following keywords: "Invasive Pulmonary Aspergillosis", "Neuroaspergillosis", "Invasive Aspergillosis", "Severe fungal infection", "Africa", "Epidemiology", "Risk factors", "Predisposing factors", "Laboratory diagnosis", and "Treatment". The Boolean operators "AND" and "OR" were used to combine these keywords.

The list of references of eligible articles and Google scholar database were also checked in order to search for possible eligible articles.

2.2. Inclusion and exclusion criteria

Any article published in English or French reporting invasive aspergillosis in African countries, based on primary data was eligible for this systematic review. An article was excluded if it was protocol, commentary article, conference paper, abstract, thesis, and if the study population was outside African countries. No restriction was imposed on the publication date and the study design.

2.3. Study selection, data extraction, and data synthesis

The titles, abstracts, and relevance full-text of identified unique reports were independently screened by two reviewers. Discrepancies were discussed and resolved by involving an independent third reviewer.

The extracted data were synthesized according to the country, study design, clinical form, incidence/prevalence, predisposing conditions, causative agents, diagnostic tools, management strategy, and case fatality rate.

3. Results

3.1. Search results

A total of 1864 citations were identified from PubMed (n = 769), AJOL (n = 135), ScienceDirect (n = 960) and Cochrane library (n = 0), of which 214 were found to be duplicates with Zotero software and excluded. Of the 1650 screened, 1594 were excluded after reading the titles and abstracts. Of the 56 full-text articles reviewed, 39 were excluded, based on eligibility criteria. Twelve additional articles (4 identified through references of eligible articles and 8 via Google scholar) were also included. Finally, 29 articles were considered for this systematic review (Fig. 1).

3.2. Epidemiology and diagnostic tools

3.2.1. Case reports

Six case reports reporting ten cases of IA were included in this systematic review (Table 1), including two cases reports in Western Africa [10,11] and four in Northern Africa [12–15]. Two case reports reported three cases of invasive pulmonary aspergillosis caused by *A. fumigatus* [13], *A. flavus* and *A. terreus* [15]. The diagnostic tools used were standard mycology technique [13,15], computed tomography (CT) scan [15], immunology (galactomannan antigen detection) and polymerase chain reaction (PCR) [15]. One sino-orbital aspergillosis with central nervous system complication was diagnosed by standard mycology technique[11]. Two disseminated invasive aspergillosis were diagnosed by histological examination [10,12], standard mycology technique, CT scan, and immunology [12]. Finally, four invasive rhinosinusitis with orbital extension caused by *A. flavus* were identified by CT scan, standard mycology technique, histology, and immunology (serology) [14].

3.2.2. Observational studies

Five observational studies were included in this systematic review (Table 2), including three in Northern Africa [16–18], one in Southern Africa [19] and one in Eastern Africa [20]. Four of these studies were prospective studies [16–19] and one was retrospective study [20]. The patients included in these observational studies were children with severe combined immunodeficiency or neutropenic cancer [16], patients with acute myeloblastic leukaemia (AML) or acute lymphoblastic leukaemia (ALL) and in whom a profound post-chemotherapy aplasia (neutrophils < 500/μL for more than 10 days) was diagnosed [17], and all neutropenic patients who had febrile episode and neutrophils < 500 per μL more than 10 days were observed [18]. The sex ratio were 0.83, 1, 1.23, 1.69 and 2.33 respectively for Gheith et *al.* [17], Wong et *al.* [19], Hadrich et *al.* [18], Kwizera et *al.* [20] and El-Sayed et *al.* [16]. The median age were respectively 28 years for Kwizera et *al.* [20], 36 years for Wong et *al.* [19] and 38 years for Hadrich et *al.* [18]. El-Sayed et *al.* [16] and Gheith et *al.* [17] respectively reported a median age of 48 months and a mean age of 27.7 years.

Invasive pulmonary aspergillosis was the main clinical form reported [17,19,20]. One case of invasive ethmoiditis with periorbital extension was also reported [17]. Two studies in Tunisia used the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) criteria [21] to classify suspected IA cases as proven, probable, and possible IA [17,18].

The diagnostic tools used were CT scan, standard mycology technique, immunology (galactomannan antigen detection) and real time PCR [17,18]. No proven cases were reported [17,18]. The prevalence of IA in Tunisia were respectively 13.14% (23/175) [17] and 27.62% (29/105) [18]. In Egypt, the prevalence of IA was 20% (6/30) [16]. The prevalence of IA based on histology examination was 2.6% in South Africa [19] and 1.15% in Uganda [20]. The main species identified in these observational studies were *A. flavus* and *A. niger* [17,18]. *A. fumigatus* was rarely identified as the causative agent of IA [17,18]. Other *Aspergillus* species such as *A. ochraceus, A. tubingensis,* and *A. westerdijkiae* were also identified in some studies [17,18].

3.3. Risk factors

3.3.1. Case reports

The predisposing conditions identified were antibiotic therapy [10,15], HIV/AIDS [13], cytomegalovirus (CMV) infection, renal transplant recipients, and renal failure [15]. One immunocompetent patient with IA was reported in Nigeria [11].

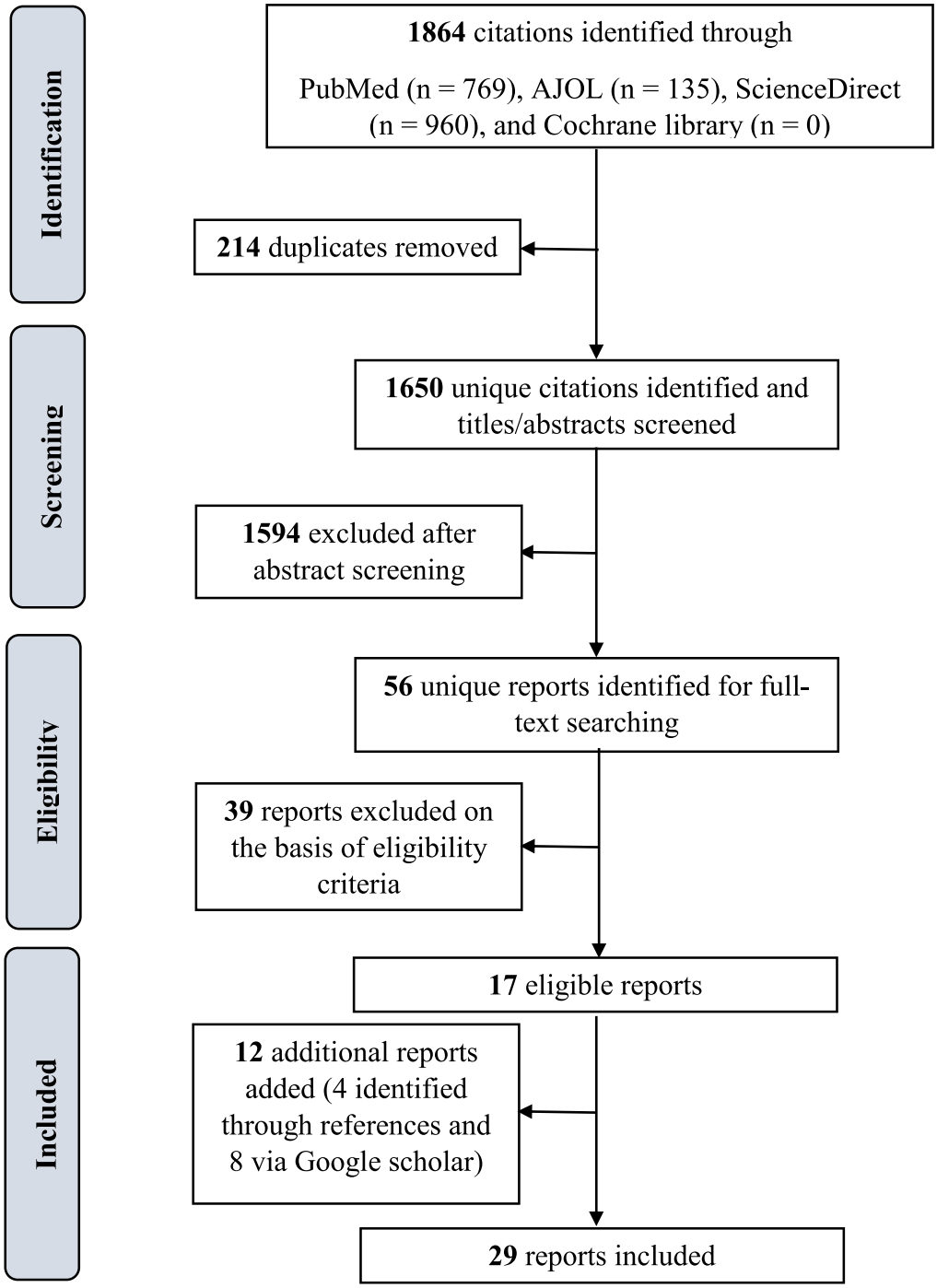

Fig. 1. flowchart of articles selected for the systematic review of invasive aspergillosis in Africa, adapted from the PRISMA guidelines [9].

3.3.2. Observational studies

The main predisposing condition identified was neutropenia [16–18]. Other predisposing factors identified were HIV/AIDS [20], severe combined immunodeficiency [16], Hodgkin's lymphoma, and bronchiectasis [19].

3.4. Management, fatal case, and antifungal resistance

3.4.1. Case reports

In the therapeutic management of IA, azoles particularly voriconazole and itraconazole, were the most antifungals drugs used [12,14,15] sometimes associated with surgery [12]. Conventional amphotericin B has also been used and then changed to voriconazole in case of treatment failure. Concerning the case reported in Nigeria, the diagnosis of IA was made after the patient died [11]. In this study during the process of clinical and biological diagnosis, no suspicion of IA was evoked until the death of the patient [11]. Among the ten IA cases reported in the six case reports, only one successful treatment (survivor) with voriconazole was reported [15].

3.4.2. Observational studies

Conventional amphotericin B or voriconazole alone or conventional amphotericin B then switched to voriconazole were the antifungal regimens used to manage the IA [17]. One of the regimens used in the management of IA was to start antifungal therapy only after a failure of broad-spectrum antibiotic therapy [16]. The case

Table 1
Case reports of invasive aspergillosis in Africa.

Country	Authors	Clinical spectrum	Number of IA	Predisposing conditions	Causative agents	Diagnostic tools	IA management	Case fatality rate
Ghana	Aleksenko et *al.*	Disseminated invasive aspergillosis	1	Prolonged antibiotic	*Aspergillus* spp	Histology	NA[1]	Died
Nigeria	Onyekonwu et *al.*	Sino-orbital aspergillosis with central nervous system complication	1	No predisposing factor identified in an immunocompetent adult	*Aspergillus* spp	Standard mycology	Surgery + ketoconazole	Died
Algeria	Bakhti et *al.*	Disseminated invasive aspergillosis	1	Chronic granulomatous disease	*A. nidulans*	Standard mycology, CT scan, histology andImmunology	Surgery + voriconazole	died
Morocco	El Hakkouni1 et *al.*	IPA[2]	1	HIV/AIDS	*A. fumigatus*	Standard mycology	NA	died
Sudan	Ahmed et *al.*	Invasive rhinosinusitis with orbital extension	4	NA	*A. flavus*	Standard mycology, CT scan, histology and serology	Itraconazole	NA
Tunisia	Trabelsi et *al.*	IPA	2	Renal transplant recipients, CMV infection	*A. terreus*	Standard mycology, galactomannan antigen and PCR	Voriconazole	Favorable
				Broad spectrum antibiotics, renal failure	*A. flavus*	Standard mycology, galactomannan antigen and PCR	Conventional amphotericin B and then voriconazole	Died

[1] NA: Not available [2]IPA: Invasive pulmonary aspergillosis.

fatality rate was 60.87% (14/23) and 68.69% (20/29) respectively for Gheith et *al.* [17] and Hadrich et *al.* [18].

No antifungal sensitivity test was performed before administration of the antifungal drug in any of the case reports and observational studies included in this systematic review.

3.5. Estimated burden of IA in Africa

3.5.1. Epidemiology

Eighteen studies estimating the burden of IA in Africa (Table 3) were found including two in Northern Africa [22,23], five in Western Africa [24–28], three in Central Africa [29–31], five in Eastern Africa [32–36], and three in Southern Africa [37–39]. The IA incidence per 100,000 inhabitants ranged from 7.1 to 10.7 in Northern Africa [22,23] and from 0.3 to 6.25 in Western Africa [24–28]. This incidence varied from 3.2 to 6.9, 0.05 to 10.9, and 4.8 to 16 respectively in Central Africa [29–31], Eastern Africa [32–36], and Southern Africa [37–39]. The estimated burden of IA did not take into account the clinical spectrum of aspergillosis, the fungal species involved in the occurrence of these aspergillosis, and the case fatality rate attributable to these IA.

3.5.2. Risk factors

Specific populations at risk included mainly hematological malignancies; HIV/AIDS, lung cancer; chronic obstructive pulmonary disease (COPD), and intensive care unit (ICU) patients were used to estimate the burden of IA [22–39].

4. Discussion

The increase of IA cases worldwide is correlated to the increase of patients with specific risk factors [3,4]. Despite the presence of some of these risk factors in Africa [22–39], little data on IA is available on this continent. This could be explained partly by the difficulties to diagnose IA or by the constraints of financial resources and the lack of qualified human resources in medical mycology field. This systematic review showed the presence of IA in Africa [10–20] and in case of lack of local data, the assuming made based on predisposing factors showed the presence of unrecognized IA [22–39]. The prevalence of IA can reach 27% [18] with a fatality rate of more than 60% [17,18]. The main clinical spectrum of IA found in this systematic review was invasive pulmonary aspergillosis [13,15,17,19,20]. These results are in agreement with existing data which showed that invasive pulmonary aspergillosis is the most common clinical form of IA accounting for 50–60% of all cases [3]. The risk factors identified in the case reports and observational studies included in this systematic review [10,12,13,15–20] were in agreement with those identified in other continents [3,4]. An immunocompetent patient in whom the diagnosis of IA has been made after his death was reported in Nigeria [11]. This data could raise the challenges of diagnosing invasive aspergillosis in immunocompetent patients in whom the index of suspicion of IA is very low. Nevertheless, an unidentified underlying immunosuppression should also explain the occurrence of IA in this patient. One of the regimens used in the management of IA was to start antifungal therapy only after failure of broad-spectrum antibiotic therapy [16]. This strategy led to a delay in the administration of an effective antifungal drug which was potentially fatal for the patient. In some cases [11], the hypothesis of IA is not even evoked because of the non-specificity of the clinical signs and the low awareness of medical personnel on the burden of IA on patients at risk. The management of IA could also be compromised by the unavailability of effective antifungals in some countries in Africa [11], which contributes to the delay in the administration of an effective antifungal. *Aspergillus* section *Flavi* and *Nigri* were the main *Aspergillus* species identified in case of IA in Africa, while *Aspergillus* section *Fumigati* was uncommon [13–15,17,18]. Similar data have already been reported by Khairallah et *al.* in Saudi Arabia who had identified *A. flavus* as the main aetiological agent of IA [40]. However, these findings are different from those conducted in developed countries where *Aspergillus* section *Fumigati* was responsible for more than 80% of IA [41,42]. The reasons favoring the predominance of a specific *Aspergillus* species in the occurrence of IA in a specific area remain unknown [43]. Nevertheless, it has been observed that an increase in the mean concentrations of conidia of a specific *Aspergillus* species in the hospital indoor air lead to an increase number of IA cases due to this species in immunocompromised patients [44]. The concentrations in the air of these specific *Aspergillus* species conidia in the environment are determined by climate and geographical factors [43]. These data show the flexibility of *Aspergillus* genus to adapt to several ecological niches.These data also raise the need to carry out standardized studies including different climatic and geographical profiles in order to identify the reasons of this diversity of *Aspergillus* species in the occurrence of IA depending on the area. The high case fatality rate observed in Africa [17,18] could be explained by a diagnostic and

Table 2
Observational reports on invasive aspergillosis in Africa.

Country	Authors	Period of data collection	Clinical spectrum	Samplesize	Sex ratio	Age	Prevalence	Predisposing conditions	Causative agents	Diagnostic tools	IA management	CFR[1] n/N (%)
Egypt	El-Sayed et *al.*	Prospective	NA	30	2.33[2]	Median[2] =48 months	20%	SCID[3] and neutropenia	NA	PCR	Antifungal therapy after a failure of antibiotic therapy[4]	NA
Tunisia	Gheith et *al.*	Prospective	IPA[5]Invasive ethmoiditis with periorbital extension	175	0.83[2]	Mean[2] =27.7 years	13.14%	Neutropenia	*A. niger*; *A. flavus*, *A. tubingensis*, *A. fumigatus*, *A. westerdijkiae*, *A. ochraceus*	Standard mycological, CT scan, galactomannan antigen and PCR	Antifungal therapy was based on amphotericin B or voriconazole, or both	14/23 (60.87)
Tunisia	Hadrich et *al.*	Prospective	NA	105	1.23[6]	Median[6] =38 years	27.62%	Neutropenia	*A. flavus*, *A. niger*, *A. ochraceus*, *A. fumigatus*	Standard mycology, CT scan galactomannan antigen and PCR	NA	20/29 (68.69)
South Africa	Wong et *al.*	Prospective	IPA	39	1[2]	Median[2] =36 years	2.56%	Hodgkins Lymphoma	NA	Histology (postmortem)	NA	NA
Uganda	Kwizera et *al.*	Retrospective	IPA	697	1.69[2]	Median[2] =28 years	1.15%	Bronchiectasis,and HIV/AIDS	NA	Histology	NA	NA

[1] CFR: Case fatality rate [2]Statistic parameters calculated based on overall study population [3]SCID: Severe combined immunodeficiency [4]The type of antifungal therapy not clearly specified in the study [5]IPA: Invasive pulmonary aspergillosis [6]Statistic parameters calculated based only on patients diagnosed with IA.

Table 3
Estimated burden of invasive aspergillosis in Africa according to the main risk factors.

Country	Authors	Number of IA per Underlying Disorder per Year				Total burden	Rate per 100,000	Predominant Groups at Risk
		HIV/AIDS[1]	Respiratory	Cancer	ICU[2]			
	Northern Africa							
Algeria	Chekiri-Talbi et *al.*	–	2818	47	–	2865	7.1	–
Egypt	Zaki et *al.*	–	–	664	8337	9001	10.7	–
	Western Africa							
Burkina Faso	Bamba et al.	–	–	54	–	54	0.3	–
Côte d'Ivoire	Koffi et al.	640	852	58	–	1550	6.15	–
Ghana	Ocansey et al.	977	210	67	–	1254	4.4	–
Nigeria	Oladele et *al.*	–	–	928	–	928	0.6	–
Sierra Leone	Lakoh et al.	104	–	40	334	478	6.25	–
	Central Africa							
Cameroon	Mandengue et *al.*	–	–	134	1041	1175	5.3	–
Democratic Republic of Congo	Kamwiziku et *al.*	380	2510	123	–	3013	3.2	–
Republic of Congo	Amona et *al.*	160	–	30	170	360	6.9	–
	Eastern Africa							
Ethiopia[3]	Tufa et *al.*	–	–	–	–	11,500	10.9	hematological malignancy, lung cancer, aids deaths, copd[4]
Kenya	Guto et *al.*	–	–	239	–	239	0.6	–
Malawi	Kalua et *al.*	1080	–	106	–	1186	6.7	–
Mozambique[3]	Sacarlal et *al.*	–	–	159	–	159	0.6	Hematological malignancy
Tanzania[3]	Faini et al.	–	–	–	–	20	0.05	Hematological malignancy
	Southern Africa							
Namibia	Dunaiski et *al.*	108	1	15	259	383	15.4	–
South Africa[3]	Schwartz et al.	–	–	–	–	3885	4.8	hematological malignancies; allogeneic hsct[5], kidney sot[6], lung sot, heart sot, liver sot, and lung cancer; patients dying of hiv; and copd patients
Zimbabwe	Pfavayi et *al.*	800	19	46	1582	2448	16	–

[1] HIV/AIDS: Human immunodeficiency virus/Acquired immunodeficiency syndrome [2]ICU: Intensive care unit [3]The IA burden was made by taking into account all predisposing groups at risk [4]COPD: Chronic obstructive pulmonary disease [5]HSCT: Hematopoietic stem cell transplantation [6]SOT: Solid organ transplantation.

therapeutic delay [17] but also by the unavailability of some effective antifungal treatments [11].

5. Conclusion

This systematic review provided evidence of the existence of invasive aspergillosis cases in Africa and especially a high rate of undiagnosed invasive aspergillosis cases. This systematic review also showed the epidemiological difference between the invasive aspergillosis cases in Africa from those of developed countries, hence the need to assess the epidemiology of these invasive fungal infections in this continent where the number of patients at risk is gradually increasing.

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Authors' contributions

IWY, SND, and TR designed the study. IWY and SND selected, extracted, and synthesised data. IWY, SND, and TR wrote the manuscript. All authors revised the final version of the manuscript. All authors read and approved the final manuscript.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest. The funder of the study had no role in the design, data collection, data analysis and interpretation or writing of the report.

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