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ORIGINAL ARTICLE

Serious fungal infections in Ecuador

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Abstract There is a dearth of data from Ecuador on the burden of life-threatening fungal disease entities; therefore, we estimated the burden of serious fungal infections in Ecuador based on the populations at risk and available epidemiological databases and publications. A full literature search was done to identify all epidemiology papers reporting fungal infection rates. WHO, ONU-AIDS, Index Mundi, Global Asthma Report, Globocan, and national data [Instituto Nacional de Estadística y Censos (INEC), Ministerio de Salud Pública (MSP), Sociedad de Lucha Contra el Cáncer (SOLCA), Instituto Nacional de Donación y Trasplante de Órganos, Tejidos y Células (INDOT)] were reviewed. When no data existed, risk populations were used to estimate frequencies of fungal infections, using previously described methodology by LIFE. Ecuador has a variety of climates from the cold of the Andes through temperate to humid hot weather at the coast and in the Amazon basin. Ecuador has a population of 15,223,680 people and an average life expectancy of 76 years. The median estimate of the human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) population at risk for fungal disease (<200 CD4 cell counts) is ~10,000, with a rate of 11.1% (1100) of histoplasma, 7% (700) of cryptococcal meningitis, and 11% (1070) of *Pneumocystis* pneumonia. The burden of candidemia is 1037. Recurrent *Candida* vaginitis (≥4 episodes per year) affects 307,593 women aged 15–50 years. Chronic pulmonary aspergillosis probably affects ~476 patients following tuberculosis (TB). Invasive aspergillosis is estimated to affect 748 patients (~5.5/100,000). In addition, allergic bronchopulmonary aspergillosis (ABPA) in asthma and severe asthma with fungal sensitization (SAFS) were estimated to affect 26,642 and 45,013 people, respectively. Our estimates indicate that 433,856 (3%) of the population in Ecuador is affected by serious fungal infection.

Introduction

Ecuador is located in the middle of the world on South America's west coast crossed by the Andean highlands and has a variety of climates from the cold of high mountains through temperate to humid hot weather on the coast, Galápagos Islands, and Amazon jungle. According to the latest population census, Ecuador has a population of 14,483,495 people and an average life expectancy of 76 years [1]. As fungal diseases are not reportable, exact data are not available and the current number of fungal infections occurring each year in Ecuador is not known. There is a dearth of data from Ecuador on the burden of these life-threatening disease entities, where only very few groups of scientists have reported their experiences, mainly in endemic fungal diseases [2–6].

The aim of this study was to estimate the burden of serious fungal disease in Ecuador by using the available published data on the local incidence or prevalence, or calculate their incidences by applying calculations based on international cohort studies, clinical trials, and rates of infections already documented in similar groups of patients elsewhere.

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Materials and methods

A literature search using Google Scholar, the PubMed website, Journals Online, and gray literature was done to identify all epidemiology papers reporting fungal infection rates from Ecuador. Given that there are little data on incidence rates in Ecuador generated by local studies, the density of fungal infections was calculated by using data generated in other countries using previously described methodology by LIFE [7]. Where no data existed, we used specific populations at risk and fungal infection frequencies in the populations to estimate national incidence or prevalence, depending on the condition. 2012 statistics were derived from the Instituto Nacional de Estadística y Censos (INEC); WHO, PAHO, ONU-AIDS, Index Mundi, Global Asthma Report, and Globocan were reviewed; national data of Ministerio de Salud Pública (MSP), Sociedad de Lucha Contra el Cáncer (SOLCA), Instituto Nacional de Donación y Trasplante de Órganos, Tejidos y Células (INDOT).

The number of human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) patients was obtained from epidemiological surveillance of AIDS in Ecuador published in UNAIDS [http://aidsinfo.unaids.org/] and data from MSP. Similarly, the proportions of AIDS patients presenting with *Pneumocystis* pneumonia, *Candida* esophagitis, and with cryptococcal meningitis in 2015 were calculated by estimates based on literature review of manuscripts addressing the incidence rates of such infections for a specific set of patients. *Pneumocystis* pneumonia is usually considered to be associated primarily with HIV and it is inferred that 10.7% of patients with AIDS develop this type of pneumonia [8].

Nationally representative estimates for the incidence of cryptococcosis are difficult to establish because cryptococcosis is not a reportable disease in Ecuador. According to Ruhnke et al. [9], 5% of new cases of AIDS each year develop cryptococcal meningitis. In Ecuador, according to MSP, 3546 new AIDS cases were recorded in 2014. Another analysis found that the prevalence of cryptococcal antigenemia was 2.9% among HIV patients [10].

In most populations, it is assumed that 90% of patients with late-stage HIV who are not being treated with highly active antiretroviral therapy (HAART) will develop oral candidiasis [11, 12]. Earlier data from a US cohort study showed that oral candidiasis may occur in 16% of HIV/AIDS individuals on HAART [13]. Esophageal candidiasis was based on the assumption that 20% of HIV patients with CD4 counts under 200×10^6/L who are not on antiretroviral therapy are affected by this condition, as well as 5% of those on therapy. Estimation of this annual burden is challenging if a large percentage of patients not on therapy have CD4 cell counts $>200 \times 10^6$/L [14, 15]. There are no data in Ecuador about the number of HIV-infected patients with CD4 counts $<200 \times 10^6$/L. We estimated ~10,000.

Cases of candidemia in hospitalized patients were based on the prevalence documented between November 2008 and October 2010 in three tertiary care hospitals of Ecuador as part of a multicenter study in Latin America [16]. The incidence of candidemia per 1000 admissions was 0.90 (range 0.30–1.10) and the incidence per 1000 patient-days was 0.16 (range 0.10–0.17). The population candidemia rate is estimated at 5/100,000. We assumed that 35% of candidemia episodes occur in the intensive care unit (ICU) and that the rate of *Candida* peritonitis is ~50% of the ICU candidemia rate [17, 18].

The number of tuberculosis (TB) cases (from 2011) was taken from the epidemiological surveillance registry in MSP (http://www.salud.gob.ec/wp-content/uploads/2014/05/OPS-libro-prevencion-tuberculosis.pdf). It is assumed that 22% of patients with lung cavities and 2% of those without cavities following pulmonary tuberculosis (PTB) will develop chronic pulmonary aspergillosis (CPA) [19]. Patients with PTB are expected to represent ~25% of the total number of CPA cases annually [20] and, so, the total prevalence of CPA from any cause is estimated using the national PTB figures [19].

Asthma rates in adults were obtained from multiple sources and 7% of the adult population was used for estimates [21]. The risk of allergic bronchopulmonary aspergillosis (ABPA) was estimated at 2.5% based on previous studies [22]. The rate of severe asthma with fungal sensitization (SAFS) was estimated as the worst 10% of the total asthma population, of whom at least 33% have fungal sensitization [23].

The national cancer database is produced by the National Cancer Registry of SOLCA [24], which reports that, in the period 2001–2005, tumors of the hematopoietic and reticuloendothelial systems are among the 25 most frequent malignancies, occupying fourth place (5.5%) in males and sixth place (4.5%) in females. According to the relative position of the 25 most frequent malignant tumors in males, lymphoma (6%) and leukemia (4%) are in fourth and fifth places, respectively. The data in females differ slightly, showing 4.3% in lymphoma (sixth place) and 3.6% in leukemia (eighth place). Lymphoid leukemia (56%) has been reported as the most common in the Quito general population, followed by myeloid leukemia (36%). The latter is more frequent in adults and represents 58%. A study among indigenous people in the Amazon region of Ecuador reported that leukemia was one of the most common types of cancer in that population [25]. Ecuador's data are also reported by the International Agency for Research on Cancer, through the Globocan project, showing an estimated incidence (2008) of crude rates for leukemia at 6.1/100,000; acute myeloid leukemia is the most common leukemia in adults [26]. Nine hundred and thirty cases of leukemia were registered in 2014. An estimated 1035 patients had lung cancer in 2012.

It is assumed that non-acute myeloid leukemia (AML) hematological conditions in total represent the same population incidence of invasive aspergillosis (IA) as AML patients; in each group, there is an incidence of approximately 10% [27]. Further, it is assumed that the incidence of IA in allogeneic hematopoietic stem cell transplants is 8% [27]. IA is also associated with solid organ transplantation, although the reported incidence varies by both dataset and anatomical site. The Transplant-Associated Infection Surveillance Network data suggest an IA 1-year cumulative incidence of 0.5% of renal, 2.0% of heart, 0.9% of liver, and 9.1% of lung transplants [28]. Given the size of this dataset, it provides the most precise disease rates and we have adopted these. Ecuadorian transplant data were obtained from the 2013 INDOT report on organ transplant and organ donation registry [29].

Recurrent *Candida* vaginitis (more than 4 episodes per year) was included in the context of serious infections due to its impact on quality of life as well as being a potential source for colonization by azole-resistant *Candida* strains [30]. For recurrent *Candida* vaginitis, the number of cases was based on 6% expected prevalence among women aged 15 to 50 years old [30]. According to the INEC, the population of this age group in Ecuador is 5,126,552 women.

Results and discussion

This is the first attempt to summarize epidemiological data on the prevalence of serious fungal disease in Ecuador and use these data for modeling burden. There are no epidemiology papers that have directly reported incidence, prevalence, or fungal infection rates, so every estimate is based on a previously published modeling approach that has been applied in many countries by the LIFE program [7].

In 2012, Ecuador had a population of 14,483,495 people [1]. Nowadays, Ecuador is considered an upper middle income country with a per capita gross domestic product of 5402 US dollars in 2014. Demographic data of the Ecuadorian population are presented in Table 1, including the main at-risk categories for fungal diseases.

Douce et al. described the first cases of histoplasmosis in AIDS patients in Ecuador in 2002. Most patients had pancytopenia, hepatitis, and diffuse reticulonodular pulmonary infiltrates. The fastest and most reliable diagnostic approach was bone marrow biopsy. Within 6 months, 83% of patients with disseminated histoplasmosis died [31]. In this study, histoplasmosis was the most frequent fungal disease after cryptococcosis in AIDS patients. According to the data of the study by Ortega and Zambrano [32], which included 675 people with AIDS, the prevalence of *Histoplasma capsulatum* was 11.1%, comprising 77% males and 23% females. The age range of the greatest prevalence was 30 to 39 years (43%), followed by 20 to 29 years (23%). The main risks associated with *Histoplasma* infection was place of origin (living by the coast, 45%) and occupation such as farmers and poultry workers (33%). Almost all (92%) histoplasmosis cases present with CD4 cell counts <200 cell/μL, so this number represents the greatest risk for most opportunistic infections, including oral candidiasis. Based on these data, the estimated global burden of disseminated histoplasmosis is 1110 cases in Ecuador and the estimated burden of oral and esophageal candidiasis is shown in Table 2. The estimate for the burden of oral and esophageal candidiasis in the same study was 50%.

Nationally representative estimates for the incidence of cryptococcosis are difficult to establish because cryptococcosis is not a reportable disease in Ecuador. Assuming that ~10,000 HIV/AIDS patients have <200 CD4 cell counts, *Pneumocystis* pneumonia affected at least 1070 (10.7%) patients and cryptococcal meningoencephalitis 700 (7%). The overall incidence was 0.12 to 0.4 cases per 100,000 [33]. The widespread availability of HAART in Ecuador has helped improve the immune systems of 85% of HIV patients in 2012, reducing vulnerability to infection with *Cryptococcus*. However, due to economic and political factors, the percentage of HIV patients on HAART has reduced to an estimated 70% in subsequent years. The burden (and our estimates) of oral and esophageal candidiasis in HIV patients depends partly on HAART therapy delivery.

Of the 5352 cases of TB in 2014, mostly in HIV-negative people, 3649 (79.6%) had pulmonary tuberculosis [18], using the approach taken by Denning et al., the 5-year point prevalence of CPA following TB, assuming a 22% cavitation rate following therapy. Assuming that 3175 (88%) of them survived to at least 12 months after diagnosis, we estimate that, annually, at least 133 patients develop CPA following pulmonary TB, and the prevalence over 5 years is 420 patients. It was assumed that TB was the underlying diagnosis of CPA in 20% of cases [19, 20], and, so, the total CPA prevalence is 2100 patients.

Estimates of asthma prevalence in adults are around 7% [34]. Assuming that 2.5% of asthmatics have ABPA, there will be 26,642 Ecuadorian patients with ABPA. The number of patients with SAFS was 136,404 and then 33% of these for those who are sensitized (45,013). It is likely that some overlap exists between these groups, depending on the severity of asthma in the ABPA patients and the number of SAFS patient sensitized to fungi other than *Aspergillus*. ABPA is an important complication of cystic fibrosis, but the average survival of patients with CF in Ecuador is 9.5 years (Table 2).

According to the National Bureau of Statistics and Analysis of Health Information Ministry of Public Health of Ecuador, 31,214 outpatients were seen in consultation with chronic obstructive pulmonary disease (COPD) in 2013 [35]. The COPD burden in Ecuador is estimated as 228,355 (Table 1). Recently, over 10% of patients with COPD were found to be sensitized to *A. fumigatus* and this was associated

Table 1 Demographic data for the calculation of fungal-related diseases in Ecuador

Population	
Population data (year 2012 INEC): 14,483,495	
Population living outside urban zones: 5,392,713	
Urban population: 67.5% of the total population (2011)	
Rate of urbanization: 2.13% annual rate of change (2010–2015 est.)	
Female sex: 7,305,812	
Of childbearing age (15–45 years): 1,065,658	
Male sex: 7,177,683	
Women and men over 40 years old: 4.262.630 (29%)	
Children: 4,528,425 (28.5%)	
HIV and AIDS estimates (2015) [36]	
New AIDS cases	3546
Deaths due to AIDS	<1000
HIV + on antiretroviral therapy (HAART)	25,900
Patients at risk (CD4 count <200 and who developed AIDS)	No data
Leukemia, transplant, and other immunocompromised patients for the year 2014	
Leukemia	939 (4% of all cancers excluding NMSC)
All cancers excluding NMSC	23,360
Allogeneic hematopoietic stem cell transplantation (2015)	33
Solid organ transplant 2015 year:	
Renal transplant procedures	118
Lung transplant procedures	0
Heart transplant procedures	0
Liver transplant procedures	14
Corneal transplant procedures	156
Pulmonary diseases	
Tuberculosis	5352
Pulmonary tuberculosis	3649
Annual incidence	38.2/100,000
HIV-positive TB patients	637 (13%)
Lung cancer	1035
Chronic obstructive pulmonary disease	
Prevalence (for patients over 40 years old)	228,355
Chronic obstructive pulmonary disease admissions to hospital per year	4023
Consultations and outpatient care	31,214 patients
Asthma	
In adults >40 years old	298,384
In adults (aged 18–45 years)	1,065,658
All adults	1,364,042
Cystic fibrosis	
Total registered	178
Average survival	9.5 years
Critical care and surgery cases (2012 year)	
Critical care beds nationally	781 (3%)
Overall hospital admissions	1,153,237
Peritoneal dialysis patients	9635

NMSC Non-melanoma skin cancer, *HAART* highly active antiretroviral therapy, *INEC* Instituto Nacional de Estadística y Censos, *HIV* human immunodeficiency virus, *AIDS* acquired immune deficiency syndrome, *TB* tuberculosis, *CD4* cluster difference 4

Table 2 Serious fungal burden infections in Ecuador

Type of disease	Serious invasive fungal infections	Predominant groups at risk	Risk population size	Affected patients
HIV/AIDS, 37,000	Pneumocytosis	HIV/AIDS <200 CD4	5000	535
	Histoplasmosis	HIV/AIDS <200CD4	5000	550
	Cryptococcosis	HIV/AIDS <200CD4	5000	350
	Oral candidiasis	Those on HAART	25,900	4144
	Oral candidiasis	Not on HAART	11,100	9990
	Esophageal candidiasis	Those on HAART	25,900	1295
	Esophageal candidiasis	Not on HAART	11,100	2220
Transplantations	*Aspergillus* infections	Hematopoietic stem cell transplantation	33	3
		Renal	118	1
		Hepatic	14	1
		Lung	0	0
		Heart	0	0
		All transplantations excluding corneal transplant	165	5
Leukemia	Aspergillosis	Leukemia (6.1/100,000)	930	124
Tuberculosis	CPA	Pulmonary TB	3649	420
Chronic respiratory disease	CPA	COPD, asthma, pneumothorax, lung surgery, sarcoidosis, etc.	>530,000	1680
COPD	Invasive aspergillosis	Total of COPD	228,355	594
Cystic fibrosis	ABPA	Cystic fibrosis patients	178	13
Asthma	ABPA	Asthma ≥40 years	298,384	26,642
		SAFS	136,404	45,013
Candidiasis	Oral candidiasis	Cancer diseases	23,400	9945
	Candidemia	Incidence per 1000 admissions: 0.90	1,153,237	1037
Non-serious invasive fungal infection		Recurrent *Candida* vaginitis (women >15 to 50 years old)	5,126,552	307,593
Total burden				433,856

with worse pulmonary function [37], so we expect 22,835 patients with COPD and "allergic" or chronic aspergillosis.

In a recent review of oral fungal infections in patients receiving cancer therapy, for all cancer treatments, the weighted prevalence of clinical oral fungal infection was found to be 7.5% pretreatment, 39.1% during treatment, and 32.6% after the end of cancer therapy [9]. These rates may differ each year but may be used as an estimate for current calculations. Each year, 6000 new cancer diseases (including hematological cancers) are recorded. Assuming that the majority of cancer patients (>90%) receive anticancer treatment, 450 (pretreatment) to 2100 (35% during/after cancer treatment) episodes of oral candidiasis can be calculated, resulting in a total of 2550 episodes each year.

The most important risk factor for IA has historically been neutropenia, and we estimate 124 cases of IA in leukemia patients. According to the 2015 INDOT data in Ecuador, there were 322 transplants (Table 2). We estimate the incidences of IA in allogeneic hematopoietic stem cell transplant as 3 and 1 cases after renal transplantation. Assuming a 20% hospital admission rate for COPD and a 1.3% IA rate among the admitted patients, we anticipate 594 cases of IA complicating COPD. We would expect a small number of IA cases in those with lung cancer, about 27, based on data from China.

The incidence of bloodstream infections in Latin America varies between 1.2 and 5.3 (0.06 to 0.39 cases per 1000 patient-days) [16]. Preliminary data in three hospitals in Ecuador showed an incidence rate of 0.90 cases per 1000 admissions and 0.16 cases per 1000 patient-days. *Candida albicans* was the most common species (52.2%), followed by *C. parapsilosis* (30.4%) and *C. tropicalis* (10.9%) [16].

A 6% rate was assumed in women to have recurrent vaginal candidiasis (four or more episodes per year), which correlates with 308,000 Ecuadorian women with recurrent vaginal thrush in any one year. A study of 213 adolescent girls in a tropical area of Ecuador found vaginal candidosis in 24% [38]. An internet survey in five European countries and the USA found a rate of 9% of recurrent vulvovaginal candidiasis,

but it is likely that many overdiagnose this and mistake it for bacterial vaginosis and other problems. Therefore, we have arbitrarily reduced the rate to 6%.

In Latin America, the causes of the increase in asthma are associated with urbanization; in Ecuador, 68% of the population live in urban zones, many having migrated from the rural areas. Rodriguez et al. sought to examine the relationship between asthma prevalence and level of urbanization in 59 small rural communities in transition from northern Ecuador. With a total of 4183 questionnaires administered to children and adolescents, the percentage coverage in the communities was about 95% of the study population. The average prevalence of asthma was found to be 10.1%, with a large variation of 0.0 to 31.4% [39]. ABPA rates may be higher in rural areas.

As in Peru and Bolivia, Ecuador artisanal mining is focused primarily on finding gold, but some other mineral mining goes on. In Ecuador, some 1500 children work in mining and 22,950 are at risk from working in mines. Often, children and adolescents work in the mines and quarries after their school classes or during their vacation, but stop when the whole family switches activity, such as agriculture [40]. Therefore, the number of cases of asthma and ABPA is probably higher. These occupations probably also contribute to the COPD burden.

It is considered that, for every one million, there are 5000 workers with occupational asthma [39]. If the economically active population in Ecuador is 8,278,922, we expect 41,395 workers to have occupational asthma [41]. Some of these will be attributable to fungal exposure, but it is difficult to estimate how many.

Approximately 8.5 million people who live in Ecuador are in risk areas for endemic fungal infection diseases. Tropical and subtropical areas where transmission exists or may exist, these risk areas are in almost all provinces. In other words, 61% of Ecuador's population live in areas with endemic mycoses such as histoplasmosis, paracoccidioidomycosis, sporotrichosis, and chromoblastomycosis. None are reportable diseases in Ecuador and we are unable to estimate the incidence of prevalence, in people not infected with HIV.

Although fungal infections occupy an important place in infectious processes with a high burden of morbidity and mortality, there are many limitations for acute diagnosis of fungal diseases in Ecuador. Limitations in reagents for the diagnosis of these diseases are frequent. Conventional diagnostic tests, such as direct microscopy, histopathology, and culture, are routinely used, but not galactomannan, β-D-glucan, or DNA detection tests, and may have impacted on the ability to diagnose invasive fungal infections. There is a limitation of resources and expertise in the laboratories and many do not have enough specialist technicians trained on fungi. Moreover, scientific skill development and medical education on fungal diseases is necessary. Liposomal amphotericin B, flucytosine, and topical natamycin are not available in Ecuador.

Conclusion

Our estimates indicate that over 3% of the Ecuadorian population is estimated to suffer from a serious fungal infection each year (433,856). If recurrent vaginal thrush is excluded, 125,263 people are estimated to be affected. Using local data available as well as national and international literature estimates of the incidence or prevalence of fungal infections, almost half a million people are affected. This study is the first to estimate the burden of serious fungal diseases in Ecuador. We consider it is necessary to include these infections as reportable diseases.

Compliance with ethical standards

Conflict of interest JZ, DWD, APyM, MBD, LMA: nothing to declare.

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