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REVIEW

Burden of serious fungal infections in the Dominican Republic

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Summary The Dominican Republic (DR) is the second largest Caribbean nation and, with Haiti, the DR accounts for nearly three-quarters of the cases of human immunodeficiency virus (HIV) infection in the Caribbean region and the highest rates of TB in the Americas. The present study estimated the burden of serious fungal infections and some other mycoses in the DR. The data were extracted from the World Health Organization Stop Tuberculosis (WHO STOP TB) program, the Joint United Nations Program on HIV/AIDS (UNAIDS), and searches for relevant literature via MEDLINE, PubMed, MedFacts, and so on. The chronic pulmonary aspergillosis (CPA), allergic bronchopulmonary aspergillosis (ABPA), and severe asthma with fungal sensitization (SAFS) rates were derived from the asthma and TB rates. When no data regarding mycoses were available, we used specific populations at risk and the frequencies of fungal infection in each of these populations to estimate the national prevalence. Among its population of 10,090,000, we estimated that 221,027 (2.2%) have a serious fungal infection, including 158,134 women with recurrent vulvovaginal candidiasis. We estimated high numbers of 25,150 for ABPA and 34,000 for severe asthma fungal sensitization (SAFS) (250 and 529/100,000, respectively). CPA was common, with an estimated 2122 cases, of which 707 followed pulmonary TB. The annual prevalence of CPA was estimated to be 1374 cases. Four cases of histoplasmosis and several cases of chromoblastomycosis have also been reported. Pityriasis versicolor and tinea capitis are frequent in children, and

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11% have kerion. Local epidemiological investigations are urgently required to validate or modify these estimates of serious fungal infections in the DR.

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Introduction

The Dominican Republic is the second largest Caribbean nation (after Cuba), both in area and population, with 48,445 square kilometers (18,705 sq miles) and an estimated 10 million people, of which one million live in the capital city of Santo Domingo. With the exception of sub-Saharan Africa, the Caribbean region has the highest HIV prevalence in the world. The Dominican Republic (DR) and Haiti account for nearly three-quarters of the HIV cases in this area and also exhibit the highest rates of TB in the Americas according to the World Health Organization [1]. Some researchers have estimated that between 6 and 11 percent of those with TB in the DR are also infected with HIV [1], which presents a dual challenge. La Romana is the third largest city in the DR and is located in one of the regions that is most seriously affected with HIV due to the high number of disenfranchised Haitians. The incidence of chronic obstructive pulmonary disease (COPD) in the DR is 0.5 per 1000 of the population [2].

Data regarding the occurrence of fungal infections in the Caribbean Region are scarce. However, there have been several reports of occurrences of mycoses in Cuba. Outbreaks of histoplasmosis have been described in French and German bat researchers returning from explorations of bat caves in Cuba [3,4]. Numerous cases of chromoblastomycosis and several cases of sporotrichosis and mycetoma have been reported [5,6]. Regarding

opportunistic mycoses, a high prevalence of vulvovaginal candidiasis in pregnant women (42.3%) has been recorded [7], and a very recent review documented 97 cases of cryptococcosis, 82 of which occurred in AIDS patients and 25 in non-AIDS patients [8]. Moreover, *Pneumocystis jirovecii* pneumonia (PCP) is known to occur frequently in AIDS patients [9]. An autopsy study of 307 AIDS patients revealed invasive pulmonary aspergillosis incidence of 2.2% [10], and a case of pulmonary aspergilloma has also been reported [11]. Superficial mycoses, viz. dermatophytic infections and mycotic keratitis, have also been recognized to be frequent in Cuba [5]. The limited information that is available regarding the prevalence of mycoses in Jamaica and Trinidad and Tobago has been reviewed in recent reports [12,13]. There have only been isolated case reports of deep mycoses and other fungal infections in most other parts of the Caribbean, for example, Haiti and Barbados.

Considering the large size of the population and the high prevalence of HIV and TB in the DR, serious fungal infections, including opportunistic mycoses, should be common despite the scarcity of reports of such infections in this country. The systemic fungal infections that have been recorded in the DR include two cases of AIDS-associated histoplasmosis [14,15] and a case of *Aspergillus* meningitis that was successfully treated with itraconazole [16]. Some superficial mycoses, such as pityriasis versicolor and tinea capitis, which are caused by *Microsporum audouinii* and *Trichophyton*

tonsurans, have been reported to be common in children [17–19]. A case of eumycetoma has also been reported [20]. The present study attempted to estimate the burden of serious fungal infections in the DR.

Materials and methods

There are currently no epidemiology papers that have reported on the fungal infection rates in the DR, so every estimate is based on modeling. A simple deterministic model that was created in Excel and has consistently been applied in many countries by the LIFE program (www.LIFE-worldwide.org) was used here [12,21]. We extracted data from the WHO STOP TB program [22] and UNAIDS [23] and also searched for relevant literature via MEDLINE, PubMed, MedFacts, and several search engines using different sets of key words. Where no data existed, we used the specific at-risk populations and the fungal infection frequencies in those populations to estimate the national incidence or prevalence depending on the condition. The search for data extended over several months from 2013 to 2014. The ABPA and severe asthma with fungal sensitization (SAFS) estimates were based on a 9.97% adult clinical asthma rate [24,25], and CPA was based on the TB rates [26]. Other assumptions were based on the incidences reported in the local and international literature. The denominator included the overall DR population and the numbers of patients with HIV/AIDS and respiratory diseases.

Results

The DR population was estimated to be 10,090,000 million people in 2011 [26]; children (0–14 years) comprise 31% of the population, and 9% are >60 years old. An estimated 158,134 women experience >4 attacks of vaginal candidiasis annually (6% women 15–50 years) [27]. The burden of HIV/AIDS in 2012 was estimated to be 45,000 patients or 0.7% of adults; 27,000 of these patients have CD4 counts <350/uL, and 21,138 (78%) have been treated with antiretroviral therapy (ARVs) [28]. Moreover, there were an estimated 1700 AIDS deaths in 2013 [29]. Assuming that 50% of the untreated patients have CD4 cell counts <200/uL, then 90% (1319 patients) of the patients probably develop oral candidiasis [30]. Regarding esophageal candidiasis, an estimate of 1183 cases has been reported annually based on the assumptions that 20% of the HIV patients who are not on ARVs [28] and 5% of those who are on

ARVs [28] are infected. Assuming that 50% of those patients who are not on ARVs and have CD4 counts <200/uL progress to life-threatening opportunistic infections each year, the rate of pneumocystis pneumonia (PCP) is 80% [29,30] and the rate of cryptococcal meningitis (CM) is 10% [30]; thus, 234 PCP cases and 29 CM cases are anticipated annually in the DR population.

The adult asthma population has been estimated at an extraordinary 1 million people based on a 9.97% clinical asthma rate [24]. Using an ABPA rate of 2.5% based on other studies [25], the DR is estimated to have 25,150 adult ABPA patients (250/100,000). Assuming that 33% of the most severe adult asthmatics are sensitized to fungi, ~34,000 patients with SAFS are anticipated (529/100,000). Further, 3896 cases of pulmonary TB were reported in 2011, which resulted in an estimate of 224 new CPA cases annually and a 5-year prevalence of 707 affected people [31] assuming an annual death rate of 15%. If TB accounts for 33% of the cases [31], then the total CPA prevalence is 2122 cases in the DR (80/100,000). Invasive aspergillosis (IA) in patients with hematological malignancy is estimated to affect 61 patients assuming a 10% attack rate in acute myeloblastic leukemia (AML) patients [32] and an equivalent number in non-AML hematological patients [33,34]. Additionally, the COPD rate is estimated to be 13.4% in those over 40 years old or a total of 374,262 patients. Assuming a hospital admission rate identical to that of Trinidad and Tobago (13%) and a 1.3% rate of invasive aspergillosis in these patients [35], the estimated IA rate is 316 patients annually, with COPD as the underlying risk factor, and all of these patients are probably treated with corticosteroids [35]. There is a report of a case of *Aspergillus* meningitis that was successfully treated with itraconazole [16], but no such reports exist for invasive aspergillosis in immunocompromised patients. If the incidence of candidemia is 5/100,000 (a low international average), 505 cases of candidemia and 76 cases of post-surgical *Candida* peritonitis occur annually [36,37].

Regarding superficial mycoses in the DR, pityriasis versicolor and tinea capitis are known to be common in children [17]. In a study of tinea capitis in 84 boys and 34 girls, the predominant etiological agents were found to be *T. tonsurans* (61.16%), *M. audouinii* (24.27%), and *Microsporum canis* (11.65%) [18]. In a previous study, 11% of 481 individuals with scalp infections caused by *M. canis* had an inflammatory form of tinea capitis (kerion), and these forms were subdivided into suppurative folliculitis (11%), suppurative folliculitis with suppurative dermatitis (37%), suppurative

Table 1 Estimated burden of fungal disease in Dominican Republic.

Fungal disease	Underlying disease					Total	n/100k
	None	HIV/AIDS	Respiratory	Cancer/Tx	ICU		
Oesophageal candidiasis	?	1183	—	?	—	3805	36.7
Candidaemia	—	—	—	353	151	136	5
Candida peritonitis	—	—	—	—	76	76	0.75
RVVC (4×/year+)	158,134	—	—	—	—	158,134	3134
ABPA	—	—	25,149	—	—	25,149	249
SAFS	—	—	33,197	—	—	33,197	329
CPA	—	—	1459	—	—	1374	55
IA	—	—	—	61	?	?	0.8
Mucormycosis	—	—	—	20	—	?	0.2
CM	?	29	—	?	—	29	0.29
PCP	—	234	?	?	—	234	2.32
Histoplasmosis	?	?	?	—	—	?	?
Fungal keratitis	?	—	—	—	—	—	?
Tinea capitis	?	—	—	—	—	?	?
Total burden estimated	158,134+	5101+	59,720	434+	227+	2,293,681+	

ABPA, allergic bronchopulmonary aspergillosis; CM, cryptococcal meningitis; PCP, *Pneumocystis jirovecii* pneumonia; IA, invasive aspergillosis; CPA, chronic pulmonary aspergillosis; RVVC, recurrent vulvovaginal candidiasis; SAFS, severe asthma with fungal sensitization; ?, many cases likely in this category, but the number is not known and is inestimable with current knowledge.

folliculitis with suppurative and granulomatous dermatitis (SGD, 26%) and SGD with fibrosing dermatitis (26%) [19]. Regarding the subcutaneous mycoses, a case of mycetoma caused by *Maduralla mycetomatis* in the foot of a 42-yr-old fisherman [20] and a case of mycetoma in the scalp caused by *M. canis* [19] have been reported. Several cases of chromoblastomycosis are also known [38].

Two cases of AIDS-associated disseminated histoplasmosis in Dominican immigrants have been detected in the USA [14,15]. In another two cases of histoplasmosis in immunocompetent Italian patients, the infections were acquired in the DR [39]. However, it was not possible to estimate the burden of histoplasmosis in the DR because no data from this country exist. We were also unable to estimate the number of cases of fungal keratitis, and some estimates are incomplete, notably, those for invasive aspergillosis, because the relevant data are not available (Table 1).

Discussion

HIV/AIDS is a major public health problem in the Caribbean and the northern tip of South America. In the DR, there are approximately 62,000 patients with HIV/AIDS, and 24,000 of these patients have CD4 counts <350/uL and are not being treated [40,41]. Based on these data, it appears that serious fungal infections and opportunistic mycoses are much more frequent than presently observed. An extensive search of the literature did not reveal

any data regarding the histoplasmin sensitivity of the human population of the DR. However, a report of two AIDS-associated cases of histoplasmosis in Dominican patients [14,15] and another report of two cases of the disease in immunocompetent Italian patients who developed after visiting the DR [39] provide evidence of the endemicity of histoplasmosis in this country. With increased awareness and diagnostic acumen, several cases of the disease in immunocompromised and immunocompetent patients are likely to be detected in the DR. Cave-associated histoplasmosis has been reported in Cuba [3,4], Jamaica [12], and Trinidad and Tobago [13]. There are several caves in the DR [42]. The inside atmosphere in one of these caves is warm and humid, and these caves harbor several species of bats; thus, it would be worthwhile to investigate the presence of *Histoplasma capsulatum* in these bats and the old bat guano admixed with the soil in this cave. Skin testing of human population around and visitors to this cave might help to assess the asymptomatic *Histoplasma* infection status. Creating awareness of the possibility of clinical histoplasmosis among physicians and public health authorities in this country might lead to the detection of several cases of the disease. Reports of a single case of eumycetoma [20] and several cases of chromoblastomycosis [38] indicate the endemicities of these mycoses in the DR, and it is likely that many more undetected cases of these diseases occur in this country. Several cases of equine lymphangitic sporotrichosis were recorded in the DR as early as 1942 based on clinical features [43]. It

can be assumed that human sporotrichosis possibly exists in the DR, although no cases have been reported.

Conclusion

In the Dominican Republic (DR), there are approximately 62,000 patients with HIV/AIDS, and 24,000 of these have CD4 counts <350/uL and are not being treated. These cases account for 75% of the total HIV-infected population in the Caribbean [1]. Moreover, the DR has the highest incidence of TB in the Americas, and according to the WHO, between 6 and 11 percent of those with TB in the DR are co-infected with HIV [1]. The incidence of COPD is 0.5 per 1000 of the population [2]. In view of the aforementioned facts, the incidence of fungal infections in this country is almost certainly much higher than previously known. We have estimated that over 220,000 people in the DR probably suffer from serious fungal infections each year, and most of these cases are related to asthma, prior TB, recurrent vulvovaginal candidiasis (RVVC), and HIV infection. Local epidemiological studies, preferably in collaboration with international experts on mycotic infections, are urgently required to establish the validity of these estimates.

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Competing interests

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Ethical approval

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