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Article

Estimating the burden of serious fungal infections in Uruguay

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Abstract: We aimed to estimate for the first time the burden of fungal infections in Uruguay. Data on population characteristics and underlying conditions were extracted from the National Statistics Institute, the World Bank, national registries and published articles. When no data existed, risk populations were used to estimate frequencies extrapolating from the literature. Population structure: total 3,444,006; 73% adults; 35% women younger than 50 years. Size of populations at risk: HIV infected 12,000; acute myeloid leukemia 126; hematopoietic stem cell transplantation 30; solid organ transplants 134; COPD 272,006 (19.7% of older than 40); asthma in adults 223,431 (prevalence 9%); cystic fibrosis in adults 48; tuberculosis 613 (incidence 26.2%), lung cancer 1,400 (ASR incidence 27.4). Annual incidence estimations per 100,000: 22.4 invasive aspergillosis, 16.4 candidaemia, 3.7 *Candida* peritonitis, 1.62 *Pneumocystis jirovecii* pneumonia, 0.75 cryptococcosis, severe asthma with fungal sensitisation 217, allergic bronchopulmonary aspergillosis 165, recurrent *Candida* vaginitis 6,323, oral candidiasis 74.5 and oesophageal candidiasis 25.7. Although some under and overestimations could have been made, we expect that at least 127,525 people suffer from serious fungal infections each year. Sporothrichosis, histoplasmosis, paracoccidioidomycosis and dermatophytosis are known to be frequent but no data are available to make accurate estimations. Given the magnitude of the burden of fungal infections in Uruguay, efforts should be made to improve surveillance, strengthen laboratory diagnosis and warrant access to first line antifungals.

Keywords: epidemiology of fungal infections; infection burden; Uruguay

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1. Introduction

Uruguay is the second smallest country in South America and considered a high-income country by the World Bank. Climate is template and humid, with average temperatures of 17ºC. The Uruguayan economy is dominated by agriculture and livestock production.

Fungal infections are caused by opportunistic and non-opportunistic fungi, including the primary pathogens *Paracoccidioides brasiliensis* and *Histoplasma capsulatum*, which are endemic in the country. The recognized spectrum of fungal species is not as wide as in other Latin American countries [2], although the real magnitude of these infections is not well known. Notification of fungal infections is not mandatory in Uruguay, so there are no comprehensive registries of such infections. Some of the opportunistic invasive mycosis are probably growing as the immunocompromised population increase, due to the increase in solid organ and bone marrow transplant and the use of immunosuppressive drugs [3]. No recent publications of the current situation of these infections in our country are available.

We aimed to estimate the burden of serious infectious diseases in Uruguay, considering those that cause higher mortality and morbidity in the population.

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2. Materials and Methods

Population structure was extracted from the World Bank data for 2016 [4] and from the last national census conducted by the National Statistics Institute in 2011 [1].

Incidence of invasive fungal infections, in general, and of candidemia, in particular, were obtained from the National surveillance network for invasive fungal infections [5].

For other fungal infections, comprehensive searches of government and scientific societies communications were performed (grey literature), and published literature was searched on Pubmed, Google scholar and the Latin American search engines for scientific literature: Scielo and Lilacs. The following terms were used, both in Spanish and English: "fungal infections/invasive fungal infections + Uruguay", "cryptococcal meningitis/ cryptococcosis/ *Cryptococcus* + Uruguay", "pneumocystosis/*Pneumocystis* + Uruguay", "aspergillosis/*Aspergillus* + Uruguay", "allergic bronchopulmonary aspergillosis/ABPA + Uruguay", "severe asthma with fungal sensitization/SAFS + Uruguay", "candidemia/candidiasis/*Candida* invasive infections + Uruguay", HIV opportunistic infections + Uruguay", "histoplasmosis/*Histoplasma* + Uruguay", paracoccidioidomycosis/*Paracoccidioides* + Uruguay", "sporotrichosis/*Sporothrix schenckii* + Uruguay", "zygomycosis + Uruguay", "tinea capitis/tinea corporis/tinea pedis/dermatophytosis + Uruguay".

Data on underlying conditions were obtained from national registries on tuberculosis [6], HIV/AIDS [7], haematological malignancies [8], the national institute of highly specialized medicine (Fondo nacional de recursos (FNR) which coordinates transplantation procedures in the whole country [9]. When no data existed, risk populations were used to estimate frequencies of fungal infections, using the previously described methodology by LIFE project [10].

3. Results and discussion

The Uruguayan population in 2016 was estimated in 3,444,006 inhabitants [4] of which 73% (2,522,059) were older than 17 years, 40% were aged 40 or older (1,381,046) and 22% (757,681) were children younger than 15 [1]. Women younger than 50 represented 35% of the whole population and 67% of all women [1].

The estimated burden for serious fungal infections is shown in Table 1.

Table 1. Burden of fungal diseases according to the size of the population used to estimate it.

		Risk population size used for estimations													Rate/100,000	Accuracy of estimation
		HIV	Non-treated HIV	AML	HSCT	SOT*	Lung cancer	COPD	Asthma	CF (adults)	Tuberculosis	ICU	Other	Number of cases		
Cryptococcosis		12,000											**	25	0.75	Probably underestimated
Pneumocystis jirovecii		12,000											**	48	1.62	Probably underestimated
Invasive aspergillosis				126	30	134	1,000	272,066						771	22.4	Fair
Chronic pulmonary aspergillosis	Annual incidence										61			27	0.78	Fair
	5 year prevalence													340	2.5	Fair
ABPA									223,431	48				5,682	165	Fair
SAFS									223,431					7,491	217	Fair
Candidemia												**	**	1,130	16.4	Probably overestimated
Candida peritonitis												**		127	3.69	
Oral candidiasis			5640											2,564	74.5	Probably overestimated
Oesophageal candidiasis		12,000	5640											885	25.7	Probably overestimated
Recurrent *Candida* vaginitis													1,209,722	108,875	6,323	Probably overestimated
*Kidney, liver and heart																

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Twelve thousand people were living with HIV in 2016 [7]. Mansilla et al reported that between 1983 and 1991, 6 of 107 patients (5.6%) attending the University Infectious Diseases Service (SEIC) with AIDS, according to CDC criteria at the time [11], presented with *Cryptococcal* invasive infections. Five of the six patients were already known to be in the AIDS stage of the infection. For the sixth patient, it was the marker disease [12]. This population represented about the half of the HIV diagnosed patients at the time [13], when the whole Uruguayan population was of 2,955,241 habitants. This means the annual incidence in the 90's was 0.41 cases of cryptococcosis/100,000 habitants. Later the same author analysed a series of 172 patients attending the SEIC between 1986 and 1995. Ten percent of them (17/162) developed cryptococcosis at some point during follow up, and for 3% (5/172) this infections was the first disease indicating AIDS [13]. More recently a laboratory based study reported 147 cases of cryptococcosis (including 135 form HIV patients, 1 from an immunocompetent person and 1 from a non-HIV immunocompromised patient) from different country regions over 6 years, between 2006 and 2012 [14]. Based on this last report, assuming that all the isolates from invasive cryptococcosis were received by the author and each represents a different episode, we can estimate an annual incidence of 0.71/100,000 (25 cases/year). Nevertheless, given not all isolates will have been referred, the actual incidence is probably significantly higher. Considering that immunocompromised patients other that HIV infected contribute to the burden of cryptococcosis, we conclude that the annual incidence is at least 1/100,000. This rate is somewhat higher that observed Chile [15] and Peru [16], Latin American countries with similar rate of HIV infected population.

Forty-eight cases of *Pneumocystis jirovecii* pneumonia (PJP) were reported among HIV patients in 2016 [7]. In 2015, 157 new cases of HIV were diagnosed at AIDS stage, and 28 of them were diagnosed with PJP (18% of AIDS new cases) [17]. The annual incidence of PJP, considering only HIV patients, is estimated at 1.62/100,000. Bienvenu et al. [18] reported that the ratio of non-HIV to HIV patients diagnosed with PJP has dramatically increased (1.7 to 5.6) over the last years, with the highest risk among patients with haematological and solid malignancies. This fact coupled with technical difficulties in straightforward microbiological diagnosis indicates that the actual incidence of PJP is higher. To date, the microbiological diagnosis in Uruguay relies on microscopic examination, which requires highly experienced staff and a good management of the sample.

The annual incidence of invasive aspergillosis (IA) was estimated based on risk populations published elsewhere. Given that in 2016 the National Leukemia Registry recorded 126 cases of acute myeloid leukemia [8] and that 30 patients had allogeneic HSCT [9] and assuming a risk rate of 10% for both groups [19], the annual incidence among patients with major haematological conditions would be 0.82/100,000. Approximately 1,400 cases of lung cancer are reported each year in Uruguay [20] (age-standardised incidence 27.4/100,000) and most of them are diagnosed at a late stage [21]. Yan et al estimated that 2.6% of lung cancer patients will suffer from IA [22] which extrapolates to 34 cases in our country. If the risk for SOT is extrapolated from Pappas, 6% of heart, 4% of lung and liver and 0.5% of kidney transplants would be complicated with IA [23]. This would represent a very low number of patients (2/year). The major contribution to the burden of IA is represented by hospitalized patients with chronic pulmonary obstructive disease (COPD). In 2003 the prevalence of COPD was estimated at 19.7% in Montevideo in those aged 40 and over [24]. Different hospitalization rates have been reported for COPD patients [25-28]. We assumed the worst case scenario of 20% of COPD patients admitted to the hospital each year. It has been estimated that 1.3% of COPD patients admitted to the hospital will develop IA [29]. Based on these estimations 226,985 were affected with COPD and 707 would have acquired IA. Summing all the risk populations described above, the total annual incidence of IA in Uruguay is estimated at 22.4/100,000 inhabitants. This is the highest incidence described in Latin America [15, 16, 25, 30, 31]. We believe this is due in part to the high incidence of COPD, chronic respiratory disease and lung cancer affecting our population compared to other countries in the region. Another reason could be that IA notification is not mandatory in most countries, including Uruguay, but informal notification may be more frequent in this small country.

Other clinical presentations of aspergillosis were estimated including chronic pulmonary aspergillosis. It has been previously assumed that 22% of patients with lung cavities and 2% of those

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without cavities following pulmonary tuberculosis (PTB) will develop chronic pulmonary aspergillosis (CPA) [32]. Patients with PTB are expected to represent ~25% of the total number of CPA cases annually, given that many other pulmonary conditions predispose to CPA, including COPD [33]. In 2015 the Honorary Commission for fighting tuberculosis and prevalent diseases (CHLAEP) reported that 613 patients were affected with pulmonary tuberculosis, giving an incidence of 3.7/100,000 among HIV infected and 21/100,000 among non-HIV infected, with a total annual incidence 26.2/100,000 [6]. This means that we should expect that 27 new cases of post-PTB CPA occurred in 2016, representing an annual incidence of 0.78/100,000. Assuming a 15% mortality or surgical resection rate, the post-TB 5 year period prevalence will be 85 cases and a total CPA prevalence of 340 cases (2.5/100,000).

Clinical asthma has been estimated at 9% of the adult population [34]. This extrapolates in 223,431 inhabitants in the country. The number of patients estimated to suffer from cystic fibrosis (CF) was estimated at 220, of which 48 were older than 17 [35]. Denning et al. estimated that 2.5% of the adult asthmatic population and 15% of cystic fibrosis population will suffer from allergic bronchopulmonary aspergillosis (ABPA) [36]. In the absence of better estimations in Uruguay, we adopted these assumptions. Then, the prevalence of ABPA is about 165/100,000. Assuming that severe asthma affects 10% of all asthmatics, and that, at least, 33% of those have fungal sensitization [37] the prevalence of severe asthma with fungal sensitisation (SAFS) in Uruguayan population can be expected to be 217/100,000. There are no Uruguayan fungal sensitisation data published. Asthma mortality rate is 2.33/100,000. Eighty deaths occur annually. As most of the deaths are in adults, it is likely that at least 50% had SAFS, because of the strong association between SAFS and hospitalisation. Nearly 50% of the deaths might have been avoided, had antifungal therapy been used – an inference that needs substantial research to clarify and validate.

ABPA and SAFS are expected to be unusually high due to the large asthmatic and CF adult populations. Brazil reports a higher asthma but a smaller CF prevalence giving a somewhat higher ABPA rate. We believe that these estimations are reasonable because the risk population is well projected. There may be some duplication between the ABPA patients with severe asthma and SAFS, but the both the proportion of severe asthma and fungal sensitisation rates are conservative.

The National IFI Surveillance Network reported that in 2011 there were 0.75-1.64 cases of candidaemia/1,000 hospital admissions [5]. Using a ratio of admissions/population of 10-20/1 [38-42] the annual incidence of candidaemia for 2011 is estimated at 16.4-32.8/100,000, which represents 565-1,130 patients. A similar incidence is reported from Brazil [25]. We assumed that *Candida* peritonitis occurs in half as many patients with candidemia in intensive care unit (estimated to be about 30% of all candidaemias), as in France [43]. The estimated annual incidence is 3.69/100,000 (125 cases/year).

Oral candidiasis is estimated presuming that 90% of untreated later stage HIV patients will develop this infection, while oesophageal candidiasis would affect 20% of untreated HIV and 5% of anti-retroviral treated [44, 45]. In 2016, 47% of the 12,000 HIV patients (5,640 patients) were not under treatment. According to Matee estimations 2,565 (74.5/100,000) and 885 patients (25.7/100,000) would have developed oral and oesphageal candidiasis, respectively. Nevertheless, given that immediate treatment following diagnosis is not still the rule in Uruguay [46], it cannot be assumed that all untreated patients are at an advanced stage of immune compromise, so these figures are probably overestimations. However, similar estimates were made in other Latin American countries [16, 25, 30, 31].

Different studies show that 5-9% of adult women present each year with recurrent Candida vaginitis (rVVC) (4 or more episodes per year) [47]. In Uruguay, given a female population younger than 50 of 1,209,722 in 2016, we anticipate between 3,512 and 6,323 cases/100,000 per year of rVVC.

Sporotrichosis was the most frequent deep mycosis in Uruguay in the 80s' when armadillo hunting started to be frequent [48]. *Histoplasma capsulatum* and *Paracoccodiodes brasiliensis* infections are known to be endemic in Uruguay, the first all over the country and the second in specific regions along the main rivers [49]**.** Isolated cases have been published but it is not possible to make approximations on the burden of these diseases. Likewise rare cases of mycetoma and chromobastomycois have been seen, but there are no systematic data to estimate prevalence. Finally, dermatophytosis are known to be frequent but no recent data is available to make estimations [50].

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5. Conclusions

Overall 127,325 persons (3,715/100,000) in Uruguay are estimated to suffer from serious fungal infections each year. Immediate life-threatening invasive fungal infections accounts for 2,135 cases/year (62/100,000).

A country registry would be advisable for better accuracy, but we think this is a fair estimation of the burden of serious fungal diseases in Uruguay based on precise figures about predisposing conditions registered by local institutions/associations and on published estimated risk.

Even though we cannot say which is the most frequent fungal infection in our population, it is clear that *Candida spp.* and *Aspergillus spp.* infections in different risk populations contribute to a great burden of fungal diseases in our country. While candidaemia diagnosis relies mostly on culture and is relatively simple, *Aspergillus* diagnosis is particularly challenging for invasive disease especially and is based not only on culture, whose interpretation could be problematic, but also on serologic testing. Molecular techniques for microbiological diagnosis are becoming increasingly available in the country. This will impact on the measure of different fungal infections like cryptococcal meningitis, PJP, candidaemia and aspergillosis, but we should be careful to not overestimate by misinterpreting the results of these very sensitive new methodologies. Improving diagnostic tools and strengthening the reference laboratory would be measures that could contribute to prompt identification and treatment.

Given the magnitude of the burden of fungal infections in Uruguay, efforts should be made to warrant access to first line antifungals, some of which are not available (posaconazole, micafungin, anidulafungin) or are too expensive to be provided to all in need (caspofungin, liposomal amphotericin B, voriconazole).

Regular monitoring of the incidence of fungal infections and of those at risk may improve the accuracy of these estimates in order to generate public policies to reduce their burden.

Conflicts of interest: The authors declare no conflict of interest.

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