Eur J Clin Microbiol Infect Dis (2017) 36:965–969
DOI 10.1007/s10096-017-2920-0

ORIGINAL ARTICLE

Burden of serious fungal infections in Guatemala

N. Medina[1] · B. Samayoa[1,2] · D. Lau-Bonilla[1] · D. W. Denning[3,4] · R. Herrera[1] · D. Mercado[1] · B. Guzmán[1] · J. C. Pérez[1] · E. Arathoon[1]

Received: 21 December 2016 / Accepted: 21 December 2016 / Published online: 27 February 2017

Abstract Guatemala is a developing country in Central America with a high burden of HIV and endemic fungal infections; we attempted to estimate the burden of serious fungal infections for the country. A full literature search was done to identify epidemiology papers reporting fungal infections from Guatemala. We used specific populations at risk and fungal infection frequencies in the population to estimate national rates. The population of Guatemala in 2013 was 15.4 million; 40% were younger than 15 and 6.2% older than 60. There are an estimated 53,000 adults with HIV infection, in 2015, most presenting late. The estimated cases of opportunistic fungal infections were: 705 cases of disseminated histoplasmosis, 408 cases of cryptococcal meningitis, 816 cases of *Pneumocystis* pneumonia, 16,695 cases of oral candidiasis, and 4,505 cases of esophageal candidiasis. In the general population, an estimated 5,568 adult asthmatics have allergic bronchopulmonary aspergillosis (ABPA) based on a 2.42% prevalence of asthma and a 2.5% ABPA proportion. Amongst 2,452 pulmonary tuberculosis patients, we estimated a prevalence of 495 for chronic pulmonary aspergillosis in this group, and 1,484 for all conditions. An estimated 232,357 cases of recurrent vulvovaginal candidiasis is likely. Overall, 1.7% of the population are affected by these conditions. The true fungal infection burden in Guatemala is unknown. Tools and training for improved diagnosis are needed. Additional research on prevalence is needed to employ public health measures towards treatment and improving the reported data of fungal diseases.

The University of Manchester in association with the LIFE program at www.LIFE-worldwide.org

✉ B. Samayoa
investigacion@asi.org.gt

[1] Asociación de Salud Integral, Guatemala City, Guatemala

[2] Universidad de San Carlos de Guatemala, Guatemala City, Guatemala

[3] The National Aspergillosis Centre, University Hospital of South Manchester, Manchester, UK

[4] The University of Manchester and the Manchester Academic Health Science Centre, Manchester, UK

Introduction

Fungal infections have been increasingly recognized as a cause of serious invasive diseases [1]. These serious fungal infections often affect those with impaired immunity, despite the impact of fungal infections, they remain unrecognized, and epidemiological information is limited in the country [1, 2].

The environmental characteristics of Guatemala, make it an endemic area for certain serious fungal pathogens, including those caused by *Histoplasma capsulatum* and *Coccidioides* sp.; infections due to *Cryptococcus neoformans* and other fungal infections have also been reported [3–5]. Further, there is an increase in those at risk for fungal diseases, highlighting the importance of determining the burden of fungal infections in the country. Epidemiological data are essential in order to prioritise care, especially guiding clinical management and optimal diagnostic testing. Here we attempt to estimate the burden of serious fungal infections in Guatemala.

Methods

A full literature search was done to identify all epidemiology papers reporting fungal infections from Guatemala or Central America region, to extend the search. We estimate the burden of serious fungal infections based on the epidemiological data

available and specific populations at risk. We have estimated frequencies for adult patients, since cases in children are uncommon.

The country demographics for 2013 were obtained from the National Institute of Statistics (INE) [6]. The estimated number of HIV cases, and the proportion of HIV patients receiving antiretroviral therapy (ARV), were obtained from the United Nations Program on HIV (UNAIDS) and World Health Organization (WHO) database, for 2015 [7, 8]. Expected cases of disseminated histoplasmosis, cryptococcal meningitis, and *Pneumocystis jirovecii* pneumonia (PCP) were based on prevalence found at the time of HIV diagnosis in an urban clinic in Guatemala with 3.8%, 2.2%, and 4.7% respectively [9]. For esophageal candidiasis, the expected cases were 20% of those HIV patients not receiving ARV therapy and an additional 5% of those on ARV therapy; oral candidiasis was estimated to occur in 90% of those without ARVs [10, 11].

Estimated cases of asthma in adults were based on a population prevalence of 2.42% [12]. We used a 2.5% rate of allergic bronchopulmonary aspergillosis (ABPA) in asthma [13]. Additionally, severe asthma is generally thought to account for ~10% of the total adult asthmatics. Among those, the prevalence of severe asthma with fungal sensitization (SAFS) is estimated to be 33% [14].

The number of pulmonary tuberculosis (PTB) cases, and related deaths in 2013 were obtained from WHO [15]. Post-TB chronic pulmonary aspergillosis (CPA) was estimated with a 5-year point prevalence. We consider that from 22% of patients with cavities, 22% have CPA, and 2% of the patients who did not develop cavities presented CPA; we applied 15% of annual attrition to deduct deaths over the 5-year period [13].

For recurrent vulvovaginal candidiasis, which was defined as at least four episodes per year, the number of cases was based on a 6% expected prevalence in women between 15 and 50 years old [16]. To estimate candidemias, we have used a rate of 5/100,000. Incidence and prevalence of hematological disorders are estimated from WHO [17]. For invasive aspergillosis (IA), we used the a rate of 10% of those with acute myeloid leukemia [18], and an equal number of cases for all other haematological disorders susceptible to fungal infection. There is no transplantation done in Guatemala. With regard to chronic obstructive pulmonary disease (COPD), we have assumed the rate in Guatemala is similar to that in Venezuela with 12.1% in people ≥40 years old [19]. Also, in Trinidad and Tobago, 13% of COPD patients were admitted each year [20], and 1.3% of COPD patients admitted to hospital develop invasive aspergillosis [21].

We estimated the burden of fungal infections in Guatemala according to the methodology of the LIFE program (www.LIFE-worldwide.org). Related fungal infections caused by other filamentous fungi are unknown. We also searched for epidemiological data for other populations at risk, but no information is currently available for the country.

Results and discussion

Guatemala is a country located in Central America with 108,889 km^2. The gross domestic product per person (GDP) was $3,478, and 6.5% of GDP was spent on health. It had an estimated population of 15,438,384 in 2013 [7, 22]; population description and number of fungal infections per underlying diseases are detailed in Table 1.

HIV/AIDS-invasive fungal infections

During 2015 according to UNAIDS, the estimated number of adult people living with HIV was 53,000, of whom 30% were on ARV therapy. Assuming that 64% of adults, who are not on ARV, are immediately susceptible to fungal disease, with CD4 count <200/μl, we estimate 23,129 cases of fungal infections in adult people living with HIV; this includes disseminated histoplasmosis, cryptococcal meningitis, PCP, and oral and esophageal candidiasis (Table 1). Additionally, there were 1,700 estimated deaths from AIDS down from 3,400 in

Table 1 Population projections, HIV and TB rates, and expected fungal infection cases

Population description	*N*	%
Male	7,535,238	48.8
Female	7,903,146	51.2
Age		
<15 years old	6,236,329	40.4
>15 and <50	7,401,434	47.9
>60 years old	1,800,621	11.7
Serious fungal infections	Totals	Rate^
Cryptococcal meningitis	338	2.2
Pneumocystis pneumonia (PCP)	722	4.7
Disseminated histoplasmosis	584	3.8
Invasive aspergillosis (IA)	671	4.4
Chronic pulmonary aspergillosis (CPA)	1,484	9.6
Allergic bronchopulmonary aspergillosis (ABPA)	5,568	36
Severe asthma with fungal sensitisation (SAFS)	7,349	48
Candidaemia	772	5
Candida peritonitis	216	1.4
Oral candidiasis	13,833	89
Oesophageal candidiasis	4,437	29
Recurrent candida vaginitis	232,357	2,894+
Total serious fungal infection burden	271,577	

^Rates per 100,000 inhabitants

+ Rate per 100,000 females

2012. We have not estimated the burden of fungal infection in children with HIV, in whom PCP is probably the most common and cryptococcal disease rare.

For disseminated histoplasmosis, we estimate 705 cases among HIV people; however, histoplasmosis is the most prevalent mycosis in Central America [5]. A national study performed in the 1960s determined a histoplasmin sensitivity of 57% (23–81%) [3], placing the country as one of a very few which are hyperendemic areas. Due to the high level of exposure to this pathogen, it is plausible to expect more cases of disseminated disease in other at-risk populations, as well as more cases of acute and chronic pulmonary disease, the most common presentation among the general population. In Latin America, rates of histoplasmosis in HIV-positive patients are estimated between 2.1% and 20%, and it is considered an AIDS-defining infection in 30–75% of new histoplasmosis diagnoses [2]; rates are likely to be higher in many rural areas. Apart from case reports, one study, which evaluated risk of disseminated infection in HIV, a retrospective analysis that found histoplasmosis and tuberculosis, were the most important AIDS-related causes of death [23]. Although histoplasmosis is one of the most common and deadly opportunistic infections among people living with HIV/AIDS, it remains poorly recognized. An analysis from 2012 found only 32 reported cases of all forms of histoplasmosis by national epidemiological reports, compared with 110 cases reported by a referral laboratory.

Coccidioidomycosis represents another important endemic mycosis in Guatemala; skin surveys performed in the 1970s found an endemic area in the Motagua Valley with a high prevalence of 42%; however, cases are not frequently reported [4].

For cryptococosis, we estimate 408 cases. However, frequencies are diverse in Latin America. Cryptococcal meningitis in Mexico has been reported a prevalence rate of 28 to 200/100,000 in patients with HIV [24], the incidence rate in Rio de Janeiro, Brazil was 0.3/100,000 in 2002 and 0.68 in 2003, but in Colombia, this rate was determined to be 0.24/100,000 in general population and 3/1,000 in HIV patients [2]. In Guatemala during 2001 to 2003, 59 cryptococcal meningitis cases were found among HIV patients who presented signs and symptoms consistent with mycotic infection, almost certainly an underestimate. The strains isolated were mainly *C. neoformans* [25], which is similar to the situation in other Latin American countries, where it is reported that 85% of cases of cryptococosis are caused by *C. neoformans* [26].

Another serious fungal infection is esophageal candidiasis, which is among the more common initial manifestations of HIV immunodeficiency, especially those with advanced untreated HIV infection, and we estimated 4,505 cases. This infection is usually accompanied by oral candidiasis, which we estimated at 16,695 cases annually.

For PCP, we estimated 816 cases; however, most cases in Guatemala are clinically diagnosed based on symptoms and differential diagnosis, without laboratory confirmation. The incidence of PCP has declined substantially with widespread use of PCP prophylaxis [27].

Respiratory infections

The number of PTB survivors in Guatemala in 2011 was 2,452. This estimate was based on 3,082 PTB cases reported in 2013 and 630 deaths. We expect 157 new cases of CPA in one year, and prevalence at 5-year period was 3.2 per 100,000 inhabitants, with 495 CPA cases. This rate is similar to Mexico with 2.9, but much lower than most developing countries [13]. We have estimated the PTB-related CPA burden at one third of the total CPA burden at 1,484 cases (9.6/100,000).

Asthma prevalence among Guatemalan adults is similar to that reported in other Latin American countries such as Mexico and Ecuador, with 2.39 and 2.13 respectively [12]. Based on those asthmatic patients, we estimate 5,568 cases of ABPA, without any supportive data from the country. Other countries have reported ABPA as the third leading cause of deep mycosis in some general hospitals [2]. Of those with severe asthma, we also consider 7,349 cases of SAFS. Guatemala has a sub-tropical and tropical climate, and some important unusual airborne allergens could be present, but rates are unknown for the region. Note that there is probably 10–40% overlap between ABPA and SAFS patients, depending on the severity of asthma in ABPA and how many SAFS patients have *Aspergillus* IgE present.

Other fungal infections

The clinical presentation of *Candida* sp. infection ranges from asymptomatic or mucocutaneous candidiasis to invasive diseases. For recurrent vulvovaginal disease, we estimate 232,357 cases, in women between 15 to 50 years old. Although not usually associated with severe morbidity, recurrent vulvovaginal candidiasis is an important concern for women with HIV infection, with much misery accompanying each episode. Central America frequencies of vulvovaginal candidiasis are lacking.

Invasive diseases due to *Candida* spp. are considered a hospital-acquired infection. In Latin America, studies conducted in Mexico and Brazil have found 4% of nosocomial bloodstream infections to be caused by Candida spp. [28], and incidence rates of bloodstream fungal infections varying from 1.2 to 5.3 per 1,000 admissions. In Guatemala, a study found that 8% of infections in a Pediatric Critical Care Unit were candidaemias, with *Candida albicans* as the most frequently isolated pathogen [29]. We have used a low international rate

of 5/100,000, which equates to about 722 cases annually, and a small number of 216 intra-abdominal candidiasis cases, most occurring after intrabdominal perforation and laparatomy.

For invasive aspergillosis, we estimated 671 cases of those with leukemia (46) and COPD (625). However, IA cases derived from COPD are likely be higher in many rural areas, due to use of tobacco and the exposure to indoor woodsmoke from cooking.

Fungal infections

Conclusions

The total burden of serious fungal infections in Guatemala is unknown, but is likely to exceed 268.363 cases (1.7% of the population). Mucocutaneous *Candida* sp. infection is anticipated to be the most common mycosis, followed by fungal asthma (ABPA and SAFS). Endemic mycoses such as coccidioidomycosis and disseminated histoplasmosis also represent a significant and incompletely assessed burden, especially in those living with HIV.

Most fungal infections are unreported, and it is difficult to estimate infections among the general population or for those at risk in some cases. For example, we have not been able to assess fungal keratitis, chromoblastomycosis, pulmonary histoplasmosis, coccidioidomycosis, or tinea capitis. This lack of data also limits information about years lived with disability (YLDs), particularly in patients at rural areas, where endemic mycoses are frequent but access to health care is limited. Guatemalan epidemiological transition needs to consider fungal infections as an unsolved and additional problem to those with chronic diseases. The recognition of fungal infections as a major contributor of mortality emphasizes public health efforts in reducing the incidence and mortality of these infectious diseases.

There is a need to improve the national reporting system, in order to determine the impact of serious fungal infections, similarly to other countries in Latin America. Also, a reference mycology laboratory is necessary to implement fungal surveillance programs, provide a focus for education, and introduce new diagnostic techniques, while promoting awareness of the importance of serious fungal infections. Future studies, based on fungal surveillance programs can provide more accurate data for the country.

References

1. Hsu JL, Ruoss SJ, Bower ND, Lin M, Holodniy M, Stevens DA (2011) Diagnosing invasive fungal disease in critically ill patients. Crit Rev Microbiol 4:277–312. doi:10.3109/1040841X.2011.581223
2. Sifuentes-Osornio J, Corz-León D, Ponce-de-León L (2012) Epidemiology of invasive fungal infections in Latin America. Curr Fung Infect Rep 6:23–34. doi:10.1007/s12281-011-0081-7
3. Taylor RL, Dobrovolny CG (1960) The distribution of histoplasmin sensitivity in Guatemala. Am J Trop Med Hyg 9:518–522
4. Mayorga R, Espinoza H (1970) Coccidiodomycosis in Mexico and Central America. Mycopathol Mycol Appl 40:13–23
5. Colombo A, Tobón A, Restrepo A, Queiroz-Telles F, Nucci M (2011) Epidemiology of endemic systemic fungal infections in Latin America. Med Mycol 49:785–798. doi:10.3109/13693786.2011.577821
6. Instituto Nacional de Estadística. Indicadores Nacionales. Retrieved from: http://www.ine.gob.gt/index.php/estadisticas/tema-indicadores
7. United Nations Program on HIV (UNAIDS). Guatemala Country profile. Retrieved from: http://www.unaids.org/en/dataanalysis/datatools/aidsinfo/
8. World Health Organization (WHO). Guatemala Country profile. Retrieved from: http://apps.who.int/gho/data/node.main.617?lang=en
9. Samayoa B, Isern V, Serra L, Rivera B, Nikiforov M, Arathoon E, Casabona J (2010) Preliminary results of a prospective cohort of HIV+ patients in Guatemala. Poster presented at the meeting of AIDS, Vienna
10. Smith E, Orholm M (1990) Trends and patterns of opportunistic diseases in Danish AIDS patients 1980–1990. Scand J Infect Dis 6:665–672
11. Buchacz K, Baker RK, Palella FJ, Chmiel JS, Lichtenstein KA, Novak RM, HOPS Investigators (2010) AIDS-defining opportunistic illnesses in US patients, 1994–2007: a cohort study. AIDS 10:1549–1559. doi:10.1097/QAD.0b013e32833a3967
12. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, Boulet LP (2012) Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Pub Health 19:204. doi:10.1186/1471-2458-12-204
13. Denning DW, Pleuvry A, Cole DC (2013) Global burden of allergic bronchopulmonary aspergillosis with asthma and its complication chronic pulmonary aspergillosis in adults. Med Mycol 4:361–370. doi:10.3109/13693786.2012.738312
14. Denning DW, O'Driscoll BR, Hogaboam CM, Bowyer P, Niven RM (2006) The link between fungi and severe asthma: a summary of the evidence. Eur Respir J 27:615–628. doi:10.1183/09031936.06.00074705
15. World Health Organization (WHO). Guatemala Country profile for TB. Retrivered from: https://extranet.who.int/sree/Reports?op=Replet&name=/WHO_HQ_Reports/G2/PROD/EXT/TBCountryProfile&ISO2=GT&outtype=html&LAN=ES
16. Foxman B, Muraglia R, Dietz JP, Sobel J, Wagner J (2013) Prevalence of recurrent vulvovaginal candidiasis in 5 European countries and the United States: results from an internet panel survey. J Low Genit Tract Dis 17:340–345. doi:10.1097/LGT.0b013e318273e8cf
17. World Health Organization (WHO), Globocan 2012. Guatemala. Retrieved from: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx
18. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55:74–108. doi:10.3322/canjclin.55.2.74
19. Menezes A, Perez-Padilla R, Jardim J, Muiño A, Lopez M, Valdivia G, PLATINO Team (2005) Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. Lancet 366:1875–1881. doi:10.1186/1471-2458-9-151
20. Thorington P, Rios M, Avila G, Henry J, Haynes C, Pinto L, Seemungal T (2011) Prevalence of chronic obstructive pulmonary disease among stable chronic disease subjects in primary care in Trinidad, West Indies. J Thor Dis 3:178–182. doi:10.3978/j.issn.2072-1439.2011.03.03

21. Guinea J, Torres-Narbona M, Gijon P, Muñoz P, Pozo F, Peláez T, Bouza E (2009) Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome. Clin Microbiol Infect 16:870–877. doi:10.1111/j.1469-0691.2009.03015.x
22. World Blank. Retrieved from: http://data.worldbank.org/indicator/NY.GDP.PCAP.CD
23. Segura L, Rojas M, Peláez N, Shor-Posner G, RosaRe D, Moreno J, Klaskala W, Baum M (1997) Disseminated histoplasmosis and human virus type-1 infection: risk factors in Guatemala. Clin Infect Dis 25:343–344
24. Corzo-León D, Armstrong-James D, Denning D (2014) Burden of invasive mycosis in Mexico. Poster presented at ICAAC, Washington
25. Soto I, Vela C, Vargas R, Ortega F, Paz L, Muralles D, Arathoon E (2004) Cryptococcus spp. Infections in an urban AIDS clinic in Guatemala City. Presented at the XV International AIDS Conference, Bangkok
26. Olivares LR, Martínez KM, Cruz RM, Rivera MA, Meyer W, Espinosa RA, Martínez RL, Santos GM (2009) Genotyping of Mexican cryptococcus neoformans and C. gatti isolates by PCR-fingerprinting. Med Mycol 47:713–721. doi:10.3109/13693780802559031
27. Alison M, Jens D, Henry M, Peter D, Walzer D, Hanson T, Laurence H, Kaplan J (2004) Current epidemiology of *Pneumocystis* pneumonia. Emerg Infect Dis 10(10):1713–1720. doi:10.3201/eid1010.030985
28. Corzo DE, Cornejo DP, Sifuentes-Osornio J (2011) Surveillance of Candida spp bloodstream infections and analysis of the risk factors for death: experience in two National Institutes of Health, 2008. Presented at XXXVI Congreso Nacional de Infectología y Microbiología Clínica, Puebla, México
29. Siliezar MC (2013) Factores de Riesgo Asociados a Candidemia en la Unidad de Cuidados Intensivos Pediátricos (Tesis de maestría). Universidad de San Carlos de Guatemala