mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Original article

The burden of serious human fungal infections in Brazil

Juliana Giacomazzi,[1] Ludmila Baethgen,[1] Lilian C. Carneiro,[1] Maria Adelaide Millington,[2] David W. Denning,[3] Arnaldo L. Colombo[4] and Alessandro C. Pasqualotto[1,5] in association with the LIFE program

[1]Postgraduation Program in Pathology, Universidade Federal de Ciências da Saúde de Porto Alegre (UFSCPA), Porto Alegre, Brazil, [2]Department of Epidemiological Vigilance, Ministry of Health, Secretary of Health Vigilance, Brasília, Brazil, [3]Education and Research Centre - University Hospital of South Manchester, Manchester, UK, [4]Departament of Medicine, Universidade Federal de São Paulo, São Paulo, Brazil and [5]Molecular Biology Laboratory, Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA), Hospital Dom Vicente Scherer (HDVS), Porto Alegre, Brazil

Summary

In Brazil, human fungal infections are prevalent, however, these conditions are not officially reportable diseases. To estimate the burden of serious fungal diseases in 1 year in Brazil, based on available data and published literature. Historical official data from fungal diseases were collected from Brazilian Unified Health System Informatics Department (DATASUS). For fungal diseases for which no official data were available, assumptions of frequencies were made by estimating based on published literature. The incidence (/1000) of hospital admissions for coccidioidomycosis was 7.12; for histoplasmosis, 2.19; and for paracoccidioidomycosis, 7.99. The estimated number of cryptococcal meningoencephalitis cases was 6832. Also, there were 4115 cases of *Pneumocystis* pneumonia in AIDS patients per year, 1 010 465 aspergillosis and 2 981 416 cases of serious *Candida* infections, including invasive and non-invasive diseases. In this study, we demonstrate that more than 3.8 million individuals in Brazil may be suffering from serious fungal infections, mostly patients with malignant cancers, transplant recipients, asthma, previous tuberculosis, HIV infection and those living in endemic areas for truly pathogenic fungi. The scientific community and the governmental agencies should work in close collaboration in order to reduce the burden of such complex, difficult-to-diagnose and hard to treat diseases.

Key words: Fungal infections, Brazilian fungal burden, epidemiology, mycology.

Introduction

Fungi are commonly underestimated as agents of human disease and deaths resulting from fungal infections are often overlooked.[1] Patients with serious fungal infections commonly require admission to the hospital and may present a large variety of clinical manifestations representing diagnostic and therapeutic challenges for the health system. Different from endemic mycoses that are caused by truly pathogenic fungal agents, opportunistic fungal infections are usually associated with underlying diseases and medical procedures that may cause host immunodepression and disruption of anatomical barriers. Despite the increasing number of individuals at risk for developing or already presenting a fungal disease, this large population continue to be internationally neglected by the public and private health system.[2]

The incidence of fungal infections varies according to socio-economic conditions, geographical regions, cultural habits and the number of individual carrying risk conditions for acquiring fungal infections. In Brazil, a continental country with a population currently exceeding 200 million people, none of the human

Correspondence: Prof. Alessandro C. Pasqualotto. Molecular Biology Laboratory, Av Independencia 155, ISCMPA/HDVS, 90075-150 Porto Alegre, Brazil.
Tel.: +55 51 99951614. Fax: +55 51 32137491.
E-mail: pasqualotto@ufcspa.edu.br

Accepted for publication 3 October 2015

doi:10.1111/myc.12427

fungal infections is currently in the list of officially reportable diseases. This situation hampers the acquisition of epidemiological data and masks the real incidence of superficial and/or invasive fungal infections in the country.

The aim of this study was to estimate the burden of serious fungal diseases in Brazil by using published data available on local incidences or extrapolating their incidences by applying to local population the rates of infections already documented in similar groups of patients elsewhere. This initiative was conducted in association with the LIFE project (Leading International Fungal Education),[2] an international programme that aims to educate the health professionals, internationally, on the importance of fungal diseases.

Materials and methods

The burden of serious fungal diseases and the respective denominators were obtained from different sources. Numbers for each fungal infection were extrapolated from epidemiological studies, while the incidence rates were estimated in each specific risk groups considered in the analysis. In the absence of incidence rates generated by local studies, the density of fungal infections was calculated by using data generated in other countries.

A serious fungal infection was considered as a life threatening condition in addition to chronic and disabling infections such as recurrent superficial *Candida* infections. Dermatophytosis (such as tinea infections) and oral candidosis were not considered as serious infections, for the purposes of this study. Recurrent *Candida* vaginitis (more than four episodes per year) was included in the context of serious infections due to its impact in quality of life as well as potential source for colonisation by azole-resistant *Candida* strains.

In order to obtain appropriate denominators, official data from the Brazilian government were obtained, in addition to literature data, including the Brazilian population for the year 2011 (Brazilian Institute of Geography and Statistics – IBGE 2011 – www.ibge.gov.br); HIV/AIDS population[3–5]; number of cases of *Pneumocystis* pneumonia and cryptococcal meningoencephalitis in AIDS patients[6,7]; data on pulmonary tuberculosis (in the overall population and in HIV-infected patients), chronic obstructive pulmonary disease, asthma and cystic fibrosis[5,8–12]; number of leukaemia patients, allogeneic haematopoietic stem cell transplantation and solid transplants per year[13,14]; number of patients on peritoneal dialysis; as well as overall numbers for critical care and surgical patients, critical care beds nationally and overall admissions to the hospital.[15]

Official data on the frequency of hospitalisation for coccidioidomycosis, histoplasmosis and paracoccidioidomycosis were obtained from the Brazilian Ministry of Health, as well as the number of cases of cryptococcal meningoencephalitis.[15]

Since no official governmental data were available for pneumocystosis, aspergillosis and candidosis, assumptions of frequencies were made by estimates based on literature review of manuscripts addressing incidence rates of such infections for specific set of patients. *Pneumocystis* pneumonia cases were estimated by the assumption that 4.7% of AIDS patients at risk present with this condition, considering exclusively patients with the number with CD4 count <350 cells per mm^3 and not on antiretroviral drugs. For the estimative, it was also considered that 50% of patients expected to have CD4 counts of <200 cells per mm^3 would develop clinical manifestations of AIDS each year. Cryptococcal meningoencephalitis affected an estimated 6832 patients.[5,11] The burden of invasive aspergillosis in acute myeloid leukaemia was considered as 13.4%,[16] in allogeneic haematopoietic stem cell transplant recipients 2.3%,[16] in renal transplant recipients 0.5% and in lung transplant recipients 13.3%.[17] The number of cases of chronic pulmonary aspergillosis (CPA) was based on the study by Agarwal *et al.* [18], while allergic bronchopulmonary aspergillosis (ABPA) was calculated by assuming the presence of this condition in 2.1% of asthmatics adults[12] and 22% in adults with cystic fibrosis.[8] We also estimated severe asthma with fungal sensitisation (SAFS), by assuming that 30% of the most problematic asthmatics (severe asthma) were sensitised to fungi and had SAFS.[19] Cases of candidaemia in hospitalised patients were based on the prevalence documented between March 2003 and December 2004 in eleven tertiary care hospitals.[20] Oesophageal candidosis was based on the assumption that 20% of patients with HIV patients who are not on antiretroviral therapy are affected by this condition, as well as 5% of those on therapy (possible over-estimation if a large percentage of patients not on therapy have CD4 cell counts of >200 cells per mm^3.[21] Recurrent *Candida* vaginitis affects 5% of women in childbearing age (15–49 years).[22–24] Data on fungal keratitis, mucormycosis, sporothricosis and chromoblastomycosis were not included in this study due to the absence of relevant epidemiological data in the country.

Diseases estimates were conservative as they assumed the lowest incidence rates reported in the literature and focused only on well-defined risk populations. Assumptions were derived using the frequency of these diseases from the literature/notified and as denominators we used official data (population, respiratory diseases, cancer and immunocompromised, and number of critical care beds) as reported in official governmental publications. All data were entered into SPSS version 20.0 for analysis.

Results

In 2011, Brazil had a population of nearly 194 million people and a per capita gross domestic product of $11 208 (IBGE data from 2011 published in 2013). Demographic data of the Brazilian population for the year 2011 are presented in Table 1. Overall, there were 11 643 050 hospital admissions in that year, and 35 403 patients were in the intensive care unit. The Brazilian population estimated to be infected by the HIV was 0.3% (n = 608 230), and 30% of these patients were not on treatment with any antiretroviral therapy.[3,5] A total of 34 218 new AIDS cases were estimated to occur annually. *Pneumocystis* pneumonia affected at least 4115 HIV/AIDS patients per year, while cryptococcal meningoencephalitis affected an estimated number of 6694 AIDS patients.

Estimates for respiratory diseases (year 2011) revealed 42 466 new cases of pulmonary tuberculosis, with 14.8% occurring in HIV-infected patients. The number of asthmatic patients ageing 18–45 years was estimated to be 10 987 304; our estimates of SAFS and ABPA will therefore be underestimate as asthma also occurs in older patients. Additionally, 142 421 patients with chronic obstructive pulmonary disease were admitted to the hospital, and 197 cases of cystic fibrosis in adults were reported. Our estimates for chronic CPA, ABPA and SAFS are shown in Table 2, and total 1 001 801 affected patients. The estimate for CPA only relates to the sequelae of pulmonary tuberculosis, whereas this disease complicates many other pulmonary disorders and is likely to be at least twice as prevalent as the estimate of 12 032, and possibly as many as five times this rate.[25,26]

The number of cases of endemic mycoses who were hospitalised (coccidioidomycosis, histoplasmosis, paracoccidioidomycosis) and reported to the Ministry of Health is presented in Table 3. The incidence (/1000) based on the overall hospital admissions were 7.12, 2.19 and 7.99 respectively.

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

Description	Number	%
Population data (year 2011)		
Population	193 976 530	100.0
Population living outside urban zones	29 096 479	15.0
Female sex	98 983 648	51.0
In childbearing age (15–49 years)	54 590 492	55.1
Male sex	94 992 882	49.0
Women and men over 40 years	64 850 732	33.4
Children	47 524 250	24.5
HIV/AIDS patients		
Current total HIV/AIDS population	608 230	0.3
Those on antiretroviral therapy	425 761	70.0
Patients with CD4 count <350 and not on antiretroviral therapy	350 000	57.5
Patients at risk (CD4 count <200 and which developed AIDS)	87 500	14.4
Annual new HIV/AIDS cases	34 218	0.01
AIDS-related deaths in 2010	11 965	2.0
Respiratory diseases		
Pulmonary tuberculosis		
New cases annually	42 466	0.02
New cases of pulmonary tuberculosis per year in HIV +ve	6 270	14.8
Annual incidence	36/100 000	
Chronic obstructive pulmonary disease		
Prevalence (for patients over 40 years)	10 168 154	15.8
Chronic obstructive pulmonary disease admissions to hospital per year	142 421	1.2
Asthma		
In adults (18–45 years)	10 987 304	13.0
Cystic fibrosis		
In adults	197	0.0001
Leukaemia, transplant and other immunocompromised patients		
Acute myeloid leukaemia new patients per year	25.24/100 000	
Allogeneic haematopoietic stem cell transplantation per year	708	
Solid organ transplant per year	6 658	
Renal transplant procedures	4 957	
Lung transplant procedures	49	
Heart transplant procedures	160	
Liver transplant procedures	1 492	
Critical care and surgery cases		
Critical care beds nationally	35 403	
Overall hospital admissions (data from 2011)	11 643 050	
Peritoneal dialysis (data from 2009)	5 609	

[1]Legend: NA, Not available.

Regarding immunocompromising conditions, acute myeloid leukaemia occurred in 5/100 000 individuals in 2011, and there is an estimate of 25 244 new

Table 2 Estimated burden of fungal diseases in Brazil.

Description of fungal infection	Totals	No underlying disease/other	HIV/AIDS	Respiratory disease	Cancer + immune compromised	Critical care + surgery	Estimated incidence (100 000)
Cryptococcal meningitis	6 832	138	6 694	–	–	–	3.52
Pneumocystis pneumonia	4 115		4 115	–	–	–	4.7 (AIDS) or 2.1 (general)
Invasive aspergillosis	8 664	–	–	–	6 813	1 851	4.47
CPA post TB	12 032	–	–	12 032	–	–	6.20
ABPA	390 486	–	–	390 486	–	–	201.31
SAFS	599 283	–	–	599 283	–	–	–
Total *Aspergillosis*	1 010 465	–	–	–	–	–	211.98
Candidaemia in hospitalised patients	28 991	11 654	870		3 131	13 336	249.00
Oesophageal candidosis	57 782	–	57 782	–	?	–	29.79
Recurrent *Candida* vaginitis (≥4× per year)	2 729 525	2 729 525	–	–	–	–	–
Total *Candida*	281 628	–	–	–	–	–	–

ABPA, Allergic bronchopulmonary aspergillosis; CPA, Chronic pulmonary aspergillosis; SAFS, Severe asthma with fungal sensitisation; TB, Tuberculosis.

diagnosis of this disease in the same year. Also, 708 patients underwent allogeneic haematopoietic stem cell transplantation and 6658 were received a solid organ transplant allograft. Our estimate for invasive aspergillosis is based on these data, as well as the number of patients admitted to hospital with chronic obstructive pulmonary disease.

Estimates of the burden of serious fungal diseases in Brazil are presented in Table 3. Estimates showed 6832 cases of cryptococcal meningoencephalitis; 4115 of *Pneumocystis* pneumonia; 1 010 465 of aspergillosis (including invasive aspergillosis, ABPA and severe asthma with fungal sensitisation – SAFS); 2 816 298 of candidosis (including candidaemia in hospitalised patients, oesophageal candidosis and recurrent *Candida* vaginitis).

Discussion

This study represents the first estimative of the burden of serious human fungal infections in Brazil, contrasting official governmental data and expected number of patients, extrapolated from literature data and adjusted to the Brazilian population. Our data demonstrate the existence of a large discrepancy between the number of fungal infections notified to Brazilian Ministry of Health and their estimated occurrence in the overall population, in particular among patients with major heath conditions. The absence of accurate data on the incidence of serious fungal infections in Brazil, as well as in many parts of the world, may lead governmental authorities to exclude such diseases from their plan of priorities for health assistance abandoning a large number of risk populations that will present high rates of morbidity and mortality associated to such infections.

Table 3 Number of fungal disease notified to the Ministry of Health in the year 2011 and incidence based on overall hospital admissions (n = 11 643 050).

Fungal infection	Totals	Incidence (/1000)
Coccidioidomycosis (ICD B38)	829	7.12
Histoplasmosis (ICD B39)	255	2.19
Paracoccidioidomycosis (ICD B41)	930	7.99

Aspergillosis, candidosis and pneumocystosis cases were not reported by the Brazilian Ministry of Health; Blastomycosis and penicilliosis are not found in Brazil (Source: [15]); ICD, international classification of diseases.

The international community has recently joined efforts aiming to acknowledge human fungal infections as a serious internationally neglected health topic.[1] Since 1961, the Brazilian Ministry of Health has established a list of human diseases requiring compulsory notification. Despite an expansion of the list in recent years, reflecting the incorporation of new challenges for the public health system, invasive fungal diseases have not been an object of national epidemiological surveillance.[27,28]

Even with recognition of the ever increasing number of patients at risk for developing fungal infections, as may be demonstrated by the rising incidence of critically ill patients, cancer patients and transplant recipients developing fungal infections worldwide, the medical support provided by the Brazilian public health system to assist such population has lagged behind patients infected by other pathogens. Different from patients infected by tuberculosis, HIV and

hepatitis C that counts with good public support for the early diagnosis and treatment of their condition, patients infected by fungal infections are not under the radar of governmental authorities. Consequently, there are limitations in terms of diagnostic tools and high cost antifungal drugs provided for the medical assistance of patients with fungal infections.

For the majority of fungal infections in Brazil, few epidemiological information are available, helping poorly in providing accurate information on disease burden, given that diagnoses are often missed, notably invasive aspergillosis, CPA and *Pneumocystis* pneumonia.[29] Fungal infections continue to have a markedly negative impact on immunocompromised patients, including those with cancer, transplant recipients and individuals with HIV/AIDS. The impact of fungal diseases in both hospital and community, and its impact on public health, continues to be hamstrung.[29]

In this study, we demonstrate that a large number of individuals in Brazil may be suffering from serious fungal infections, mostly patients with malignant neoplasia, transplant recipients, asthma, previous history tuberculosis, HIV infection and those living in endemic areas for true pathogenic fungi. In order to confirm these impressive numbers, both community and hospital-based surveillance studies are urgently required.

In the last 2 years, several international studies have been submitted to scientific meetings, analysing the burden of severe fungal infections. At least 56 different countries have produced data about the burden of the most prevalent fungal infections and four manuscripts were published in scientific journals [examples in references[18,30–32]]. Compared to our data, Oladele *et al.* [30] and Rodriguez Tudela *et al.* [31] have, also, shown higher than anticipated frequencies of fungal infections. Rates of invasive and/or deep/systemic fungal infections (/100 000 individuals) were 11.8 in Nigeria, 17 in Senegal, 2.1 in Spain, 9.0 in Germany and 21.4 in Denmark.[30]

Few fungal diseases were notified to the Brazilian Ministry of Health such as coccidioidomycosis, histoplasmosis and paracoccidioidomycosis, whereas the burden of other prevalent fungal diseases in our region (i.e. chromoblastomycosis mucormycosis and sporotrichosis), is just unknown. In addition, due to difficulties in performing an accurate diagnosis it is quite possible that many male patients diagnosed with coccidioidomycosis actually had paracoccidioidomycosis, a much more common and widely distributed fungal infection. Worldwide, *Candida* species are the most prevalent agents of fungal infection, corresponding to approximately 50% of the cases, followed by *Aspergillus* spp. infections.[20,32–34] In our study, we observed that 74% of the infections were caused by species belonging to the *Candida* genus and 25% by *Aspergillus* species. It is important to note that we put together data related to episodes of invasive candidiasis with that related to recurrent mucosal candidiasis and oesophagitis, considering their potential impact in morbidity and quality of life. Dorgan *et al.* [32], studying the population of Ireland, found that 81% and 10% of the serious fungal infections are caused by *Candida* and *Aspergillus* species respectively. Another study, estimating the burden of chronic and allergic pulmonary aspergillosis in India showed, also, that there was a significant burden of ABPA, SAFS and CPA, emphasising the importance of prospective community-based studies to determine the prevalence of these disorders.[18]

Important challenges remain in the field of fungal infections, including the development of a registration system to notify these diseases in overall and high-risk population, as well as to develop and to validate point of care tests for early diagnosis of fungal infections. The available conventional diagnostic tests (i.e. serology, culture tests and histopathology) for most fungal infections provide suboptimal results in terms of sensitivity and specificity or require invasive medical procedures difficult to be performed in critically ill patients. Otherwise, molecular tests are difficult to be implemented in resource-limited countries due to the lack of well-trained laboratory staff as well financial support to acquire equipments and consumables. As a consequence, the diagnosis of fungal infections is usually late increasing rates of mortality and sequels.[35] There is a urgent need of specific public polices to incorporate new strategies for the early diagnosis of fungal infections in reference medical centres in Brazil in order to improve their capability to early diagnose invasive fungal diseases, as well as to educate medical staff on the prevention, care and treatment of a wider range of medically relevant mycoses.

This study is the first to estimate the burden of serious fungal diseases in Brazil and to provide an estimation of its impact on public health. Serious fungal infections affect more than 3.8 million Brazilians. Our results are in synchrony with recent data coming from different areas of the globe to demonstrate that the number of patients victimised by severe fungal diseases is astonishing. The scientific community as well as the governmental agencies should work in close collaboration in order to reduce the burden of such complex, difficult-to-diagnose and hard to treat diseases. Important steps are necessary: to include these serious

fungal conditions among reportable diseases, which can be done linked to results of diagnostic tests (networks that also need to be developed in Brazil) or linked to specific antifungal treatments. Additionally, to promote technical and scientific development in the area, including networks of health services, new diagnostic tools and therapeutic and disease control strategies.

References

1 Brown GD, Denning DW, Gow NA *et al.* Hidden killers: human fungal infections. *Sci Transl Med* 2012; **4**: 165rv13.
2 http://www.life-worldwide.org/fungal-diseases/ [accessed on 28 October 2015].
3 World Health Organization. Women of Childbearing age who are malnourished [WWW document], 2011. URL http://www.who.int/ceh/indicators/malnourishedwomen.pdf [accessed on 3 November 2014].
4 Fichtenbaum CL. HIV In Site, Candidiasis and HIV http://hivinsite.ucsf.edu/InSite%3Fpage%3Dkb-00%26doc%3Dkb-05-02-03 [accessed on 28 October 2015].
5 UNAIDS. Tratamento 2015. URL http://www.unaids.org/sites/default/files/en/media/unaids/contentassets/documents/unaidspublication/2013/JC2484_treatment-2015_pt.pdf [accessed on 4 February 2015].
6 Soares VY, Lucio Filho CE, Carvalho LI, Silva AM, Eulálio KD. Clinical and epidemiological analysis of patients with HIV/AIDS admitted to a reference hospital in the northeast region of Brazil. *Rev Inst Med Trop Sao Paulo* 2008; **50**: 327–32.
7 Saeed NK, Farid E, Jamsheer AE. Prevalence of opportunistic infections in HIV-positive patients in Bahrain: a four-year review (2009-2013). *J Infect Dev Ctries* 2015; **9**: 60–69.
8 Paschoal IA, de Oliveira Villalba W, Bertuzzo CS *et al.* Cystic fibrosis in adults. *Lung* 2007; **185**: 81–87.
9 Brazilian Cystic Fibrosis Registry [WWW document], 2009. URL http://www.gbefc.org.br/gbefc/REBRAFC_EN_2009.pdf [accessed on 3 November 2014].
10 Brazilian Unified Health System Informatics Department (DATASUS). Pulmonary tuberculosis (in the overall population and in HIV+ patients) [WWW document], 2011. URL http://tabnet.datasus.gov.br/cgi/deftohtm.exe?idb2011/d0202.def [accessed on 21 July 2015].
11 Brazilian Unified Health System Informatics Department (DATASUS). Chronic obstructive pulmonary disease prevalence [WWW document], 2011. URL http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sih/cnv/nruf.def [accessed on 3 November 2014].
12 Fiori NS, Gonçalves H, Dumith SC *et al.* Ten-year trends in prevalence of asthma in adults in southern Brazil: comparison of two population-based studies. *Cad Saude Publica* 2012; **28**: 135–44.
13 Brazilian Unified Health System Informatics Department (DATASUS). Acute myeloid leukemia new patients per year [WWW document], 2011. URL http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sih/cnv/nruf.def [accessed on 3 November 2014].
14 http://www.abto.org.br [accessed on 28 October 2015].
15 Brazilian Unified Health System Informatics Department (DATASUS). CNESNet, Secretaria de Atenção à Saúde [WWW document], 2011. URL http://cnes.datasus.gov.br/Mod_Ind_Tipo_Leito.asp?VEstado=00 [accessed on 3 November 2014].
16 Nucci M, Garnica M, Gloria AB *et al.* Invasive fungal diseases in haematopoietic cell transplant recipients and in patients with acute myeloid leukaemia or myelodysplasia in Brazil. *Clin Microbiol Infect* 2013; **19**: 745–51.
17 Pasqualotto AC, Xavier MO, Sánchez LB *et al.* Diagnosis of invasive aspergillosis in lung transplant recipients by detection of galactomannan in the bronchoalveolar lavage fluid. *Transplantation* 2010; **90**: 306–11.
18 Agarwal R, Denning DW, Chakrabarti A. Estimation of the burden of chronic and allergic pulmonary aspergillosis in India. *PLoS ONE* 2014; **9**: e114745.
19 Denning DW, Pashley C, Hartl D *et al.* Fungal allergy in asthma–state of the art and research needs. *Clin Transl Allergy* 2014; **4**: 14.
20 Colombo AL, Nucci M, Park BJ *et al.* Epidemiology of candidemia in Brazil: a nationwide sentinel surveillance of candidemia in eleven medical centers. *J Clin Microbiol* 2006; **44**: 2816–23.
21 Gazzard BG, Smith D. Oral candidosis in HIV-infected patients. *Br J Clin Pract Suppl* 1990; **71**: 103–8.
22 Sobel JD. Vulvovaginal candidosis. *Lancet* 2007; **369**: 1961–71.
23 Foxman B, Muraglia R, Dietz JP, Sobel JB, Wagner J. Prevalence of recurrent vulvovaginal candidiasis in 5 European Countries and the United States: results from an Internet Panel Survey. *J Low Genit Tract Dis* 2013; **17**: 340–5.
24 World Health Organization. Progress Report, Global HIV/AIDS response [WWW document], 2011. URL http://www.who.int/hiv/pub/progress_report2011/en/ [accessed on 3 November 2014].
25 Denning DW, Pleuvry A, Cole DC. Global burden of chronic pulmonary aspergillosis as a sequel to pulmonary tuberculosis. *Bull World Health Organ* 2011; **89**: 864–72.
26 Smith N, Denning DW. Underlying pulmonary disease frequency in patients with chronic pulmonary aspergillosis. *Eur Respir J* 2011; **37**: 865–72.
27 Teixeira MG, Penna GO, Risi JB *et al.* Seleção das doenças de notificação compulsória: Brazilian Ministry of Health 2014. Diário Oficial da União, Portaria 1271, 2014.
28 Brazilian Ministry of Health. Diário Oficial da União, Portaria, 1271, 2014.
29 Dignani MC. Epidemiology of invasive fungal diseases on the basis of autopsy reports. *F1000Prime Rep* 2014; **6**:81.
30 Oladele RO, Denning DW. Burden of serious fungal infection in Nigeria. *West Afr J Med* 2014; **33**: 107–14.
31 Rodriguez-Tudela JL, Alastruey-Izquierdo A, Gago S *et al.* Burden of serious fungal infections in Spain. *Clin Microbiol Infect* 2015; **21**: 183–9.
32 Dorgan E, Denning DW, McMullan R. Burden of fungal disease in Ireland. *J Med Microbiol* 2015; **64**: 423–6.
33 Mortensen KL, Denning DW, Arendrup MC. The burden of fungal disease in Denmark. *Mycoses* 2015; **58**(Suppl. S5): 15–21.
34 Cassone A. Vulvovaginal *Candida albicans* infections: pathogenesis, immunity and vaccine prospects. *Br J Obstet Gynaecol* 2015; **122**: 785–94.
35 Hayes GE, Denning DW. Frequency, diagnosis and management of fungal respiratory infections. *Curr Opin Pulm Med* 2013; **19**: 259–65.