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ORIGINAL ARTICLE

# Serious fungal infections in Peru

**B. Bustamante**[1] · **D. W. Denning**[2] · **P. E. Campos**[3]

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**Abstract** Epidemiological data about mycotic diseases are limited in Peru and estimation of the fungal burden has not been previously attempted. Data were obtained from the Peruvian National Institute of Statistics and Informatics, UNAIDS and from the Ministry of Health's publications. We also searched the bibliography for Peruvian data on mycotic diseases, asthma, COPD, cancer and transplants. Incidence or prevalence for each fungal disease were estimated in specific populations at risk. The Peruvian population for 2015 was 31,151,543. In 2014, the estimated number of HIV/AIDS and pulmonary tuberculosis cases was 88,625, 38,581 of them not on ART, and 22,027, respectively. A total of 581,174 cases of fungal diseases were estimated, representing approximately 1.9% of the Peruvian population. This figure includes 498,606, 17,361 and 4,431 vulvovaginal, oral and esophageal candidiasis, respectively, 1,557 candidemia cases, 3,593 CPA, 1,621 invasive aspergillosis, 22,453 allergic bronchopulmonary aspergilllosis, 29,638 severe asthma with fungal sensitization, and 1,447 *Pneumocystis* pneumonia. This first attempt to assess the fungal burden in Peru needs to be refined. We believe the figure obtained is an underestimation, because of under diagnosis, non-mandatory reporting and lack of a surveillance system and of good data about the size of populations at risk.

## Introduction

While candidemia and invasive aspergillosis (IA) are clearly recognized as important causes of morbidity and mortality, other mycotic agents or different clinical presentations are important in specific regions. Socio-economic and geo-ecological characteristics and size of susceptible populations are the main determinants of variations on incidence of fungal infections across the world. Peru has high rates of tuberculosis (TB) and so there are a significant number of patients with pulmonary sequela, who are susceptible to slowly progressive chronic pulmonary aspergillosis (CPA), including aspergilloma. In addition, the remarkable Peru-wide ecological diversity favors the presence of several endemic mycoses such as sporotrichosis, paracoccidioidomycosis and histoplasmosis.

The knowledge about fungal burden in Peru will help introduction of both diagnostic and therapeutic interventions to reduce morbidity and mortality. As fungal diseases are rarely the subject of surveillance, estimation of burden based on the number of patients at risk provides an approximation to the local situation. The LIFE program has grouped patients into five discrete categories, allowing estimation and comparability by underlying disease (http://www.life-worldwide.org/).

This report presents results from the first attempt to estimate the burden of fungal infection in Peru using local incidence or prevalence data or by extrapolating figures obtained for similar groups of patients in neighboring countries or elsewhere.

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✉ B. Bustamante
ana.bustamante@upch.pe

[1] Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Av. Honorio Delgado 430, San Martin de Porres, Lima 31, Lima, Peru

[2] The University of Manchester and The National Aspergillosis Centre, University Hospital of South Manchester in association with the LIFE program at www.LIFE-Worldwide.org, Manchester, UK

[3] Investigaciones Medicas en Salud, Calle Riso 390, 4to piso, Lince, Lima14, Lima, Peru

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## Material and methods

The burden of serious fungal infections was estimated using the methodology promoted by LIFE, which is extensively used around the world (http://www.life-worldwide.org/). First, we define the total population of Peru as well as the size of several communities at risk of serious or chronic fungal infection. We included recurrent vulvovaginal candidiasis (VVC) in this report because of its substantial impact on women's quality of life, while dermatomycosis was not. Incidence or prevalence data, from Peru or from neighboring countries, of each mycosis for a specific population at risk was applied to estimate the national number of cases.

The source of demographic data were the Peruvian National Institute of Statistics and Informatics' reports [1], while HIV/AIDS and TB figures were obtained from UNAIDS and the different Ministry of Health's technical offices' publications [2–4]. Because fungal infections are not notifiable diseases, we reviewed the bibliography for Peruvian data on mycotic diseases. We searched the electronic database Medline, LILACS, Google Scholar and Scopus, from 2000 to 2015 using the terms "Fungal infections", "Sporotrichosis", "Cryptococcosis", "Paracoccidioidomycosis", "Aspergillosis", "Aspergilloma", "Candidemia", "Tuberculosis", and "HIV" plus "in Peru", to identify relevant studies in English or Spanish. In addition, data from Master and Doctoral theses, congress abstract books (grey literature), and information from local experts was collected.

To infer the prevalence of recurrent VVC, it was estimated that it affects between 5 and 9% of women in childbearing age [5, 6]. For this report, we applied a rate of 6% to the 8,310,107 Peruvian women aged 15 to 49 years.

According to literature data, we assume that 45% and 20% of patients with HIV not on antiretroviral therapy (ART) will develop oral or oesophageal candidiasis respectively, and that 0.5% of those on ART will develop oesophageal candidiasis [7–10].

The annual number of candidemia cases was estimated using the rate of 5 per 100,000 habitants, 3.5 for candidemia in cancer and immunocompromised patients plus 1.5 for those in critical care or surgery, which is a mean of the 2 to 11 per 100,000 rates reported by Arendrup [11]. Although we identified a report of 1.18 cases per 1,000 admissions prospectively measured in a tertiary care referral hospital located at the capital city [12], we choose the Arendrup approach recognizing the potential poor generalization of the 1.18 figure to many of the hospitals in Peru. This tertiary care referral hospital cares for a large proportion of patients admitted into ICUs, receiving chronic dialysis and invasive procedures—central venous catheters, total parenteral nutrition and mechanical ventilation, together with chronic pulmonary diseases, and transplant recipients. Based on the report of Montravers (in France), the number of candida peritonitis cases was estimated as 50% of candidemia cases associated with critical care wards [13].

To estimate the number of CPA cases after pulmonary TB, first we used the 90% of the 2014 number of annual new pulmonary TB cases to account for TB deaths [4]. The number of CPA in cavities was calculated by applying 13%, as the proportion of patients that developed cavities as measured by Martinez et al. [14], and then 22%, which is the incidence of CPA in cavities [15]. The number of CPA post TB in patients without cavities was calculated by applying an arbitrary 2% to the proportion of TB patients that did not develop cavities (87%) [15]. Second, we estimated the five-year period prevalence of CPA assuming an annual 15% mortality or surgical cure, to account for chronicity of this condition. Finally, assuming TB is the underlying diagnosis in 80% of cases, we estimated the total number of CPA cases [16].

The number of invasive aspergillosis (IA) cases was estimated for different at-risk populations. First, we calculated the number of acute myeloid leukemia (AML) patients per year extrapolating the incidence rate of 1 in 22,818 habitants, measured for the US population (http://www.cureresearch.com/a/acute_myeloid_leukemia/stats-country_printer.htm) to the Peruvian population. We assumed that 10% of cases will develop IA and added a similar number to account for cases among patients with non-AML haematological conditions [17, 18]. Second, the number of chronic obstructive pulmonary disease (COPD) patients was estimated using the 6% prevalence among Peruvian adults ≥35 years reported by Jaganath et al. [19], and assumed a hospital admission rate of 13% as reported for Trinidad and Tobago and a 1.3% of IA among these patients (http://www.gaffi.org/media/academic-papers/) [20]. Third, the number of IA cases among lung cancer patients was estimated by calculating the 2.6% reported by Yan to the 5,540 lung cancer cases (2,779 new cases plus 2,681 five year prevalence cases) reported in Peru during 2012 [21] (http://gco.iarc.fr/today/fact-sheets-populations?population=900&sex=0). Finally, we added 0.3%, 0.8%, 4.8% and 42% of the number of renal, liver, heart and allogeneic-HSC transplant recipients respectively that will likely develop IA each year [18, 22]. The number of transplant recipients used in our estimation represents all those performed at the Social Security System (EsSalud) Hospitals [23], where most transplants are performed in Peru. IA associated with steroid immunosuppression patients was not included.

Clinical asthma rates in Peru's neighboring countries have been reported between 2.13 and 12.98 per 100,000 adults aged 18–45 [24], while history of asthma among Peruvian adults ≥35 years was reported as 3.9% by Jaganath [19]. For our estimation of adults asthmatics we used a conservative value of 4%. Estimation of ABPA assumes 2.5% of adult asthmatics develop this complication [25], while estimation of severe asthma with fungal sensitization (SAFS) prevalence assumes 33% of the worst 10% of adult asthmatics or 3.3% of

the total number of adults with asthma are affected [26]. Cases of cystic fibrosis were not considered in the estimation of ABPA because it is a very rare diagnosis in Peru.

To estimate the number of sporotrichosis cases in the hyperendemic area of Abancay, located in the Peruvian highlands, we applied an overall rate of 54 per 100,000 to the 106,214 inhabitants of this area during 2015 [1, 27]. Because sporotrichosis is also transmitted in other locations of the highlands and the jungle of Peru, as reported from a tropical diseases referential center located in the capital city of Peru, we added the six sporotrichosis cases diagnosed in this center each year [28]. In addition, we added a similar number of cases we assumed are identified each year at another eight tertiary care hospitals and in other tropical disease research centers located in Lima.

Microbiologic confirmation of *Pneumocystis* pneumonia (PCP) diagnosis is rarely accomplished in most developing countries because of unavailability of laboratory capabilities, and reported PCP prevalence among adult HIV infected patients range widely, from 5 to 60%, due to use of different diagnostic techniques. For estimation of the PCP number, we assumed 15% of new diagnosed HIV positive patients with CD4 counts <200 will present or will develop PCP. This figure is close to the 13% prevalence of PCP obtained in a study postmortem in Peruvian adult HIV positive patients [29]. Other populations at risk for PCP, including transplant recipients, corticosteroid immunosuppressed and cancer patients, malnourished children, and children with inherited immunodeficiency syndromes were not included in this estimation.

To estimate the number of patients with cryptococcal meningitis (CM), we assumed that 25% of HIV positive patients not receiving ART have CD4 counts lower than 100 cells/$mm^3$, and applied the 3.6% prevalence of cryptococcal antigenemia (CRAG+) measure in a Peruvian HIV cohort [30]. Then we assumed that 45% would develop CM, based on a rough mean of measurements (23, 60 and 50%) from Peru, Argentina and Colombia, respectively [30–32].

The annual incidence of histoplasmosis was estimated by reviewing the records of the mycology laboratory of the tropical diseases referential center referred above and calculating the average number of patients diagnosed between 2003 and July 2016. Then, we added the same number of cases to account for cases diagnosed in other health institutions, as we did for sporotrichosis.

Because paracoccidiodomycosis, mucormycosis, chromoblastomycosis and fungal keratitis are diagnosed only occasionally, they are not included in this study.

## Results and discussion

Demographic data for Peru and estimated number of asthma, pulmonary TB, HIV, COPD, lung cancer and AML cases are shown in Table 1. Estimates of fungal burden with its respective rate per 100,000 inhabitants for the different fungal infections are depicted in Table 2. Our estimate shows that both candidiasis (including recurrent VVC, oral and oesophageal candidiasis, and candidemia) and aspergillosis (including CPA, IA, ABPA, and SAFS) are the most common fungal infections in Peru. The total of 581,174 cases of serious fungal diseases that occur each year in Peru, represents approximately 1.9% of the total Peruvian population.

Our overall estimate of 1.9% of the total population affected by a serious fungal infection is similar to others reported for American countries such as Brazil, Dominican Republic, Jamaica, Mexico and Trinidad and Tobago, ranging from 2.0 to 2.4% (http://www.gaffi.org/media/academic-papers/) [33]. It is similar to the rates reported for some European developed countries, such as Denmark and Belgium (1.7 and 2.1%, respectively), and for African countries such as Senegal and Tanzania (1.6 and 2.3%) (http://www.gaffi.org/media/academic-papers/). The estimated rate for Peru is also lower than the ones reported for Spain and Germany (3 and 3.6%) (http://www.gaffi.org/media/academic-papers/).

It is important to consider that similar overall rates hide a large number of differences. For example, developed countries have higher rates of IA associated with immunosuppression (due to corticosteroid treatment, cancer and transplant recipients) and of candidemia (associated with advanced life

**Table 1** Demographic and health data used to estimate the fungal burden in Peru

| Population | Number |
|---|---|
| Total population, 2015 | 31,151,543 |
| Total adults, 2015 | 22,452,863 |
| Adults ≥35 years | 11,663,820 |
| Women aged 15–49 years, 2015 | 8,310,107 |
| HIV population, 2014 | 88,625 |
| HIV population not receiving ART, 2014 | 38,591 |
| Annual AIDS cases at risk of OIs | 9,648 |
| Pulmonary tuberculosis, 2014 (new cases) | 22,027 |
| Acute myeloid leukemia, 2015 | 1,365 |
| COPD adults ≥35 years | 699,829 |
| Lung cancer, 2012 | 5,540 |
| Renal transplant recipients, 2014 | 111 |
| Liver transplant recipients, 2014 | 23 |
| Heart transplant recipients, 2014 | 14 |
| Allogeneic-HSCT, 2014 | 48 |
| Adults with asthma, 2015 | 898,115 |
| Adults with severe asthma, 2015 | 89,811 |
| Residents in the Abancay area (2015) | 106,214 |

*HIV+* human immunodeficiency virus, *ART* antiretroviral therapy, *AIDS* acquired immunodeficiency syndrome, *OI* opportunistic infections, *HSCT* hematopoietic stem cell transplant

**Table 2** Estimated burden of serious fungal infections

| Fungal infection | Rate per 100,000 habitants | Totals | Number of fungal infections per underlying condition per year | | | | |
|---|---|---|---|---|---|---|---|
| | | | None | HIV/AIDS | Respiratory disease | Cancer + immunodeficiency | Critical care + surgery |
| RVVC | 3,201[a] | 498,606 | 498,606 | | | | |
| Oral candidiasis | 56 | 17,366 | | 17,366 | | | |
| Oesophageal candidiasis | 26 | 7,968 | | 7,968 | | | |
| Candidemia | 5 | 1,557 | | | | 1,090 | 467 |
| Candida peritonitis | 0.8 | 234 | | | | | 234 |
| CPA post TB; five-year prevalence | 9 | 2,874 | | | 2,874 | | |
| CPA all | 11 | 3,593 | | | 3,593 | | |
| Invasive aspergillosis | 5 | 1621 | | | 1,183 | 438 | |
| ABPA | 72 | 22,453 | | | 22,453 | | |
| SAFS | 95 | 29,638 | | | 29,638 | | |
| PCP | 4.6 | 1,447 | | 1,447 | | | |
| Cryptococcal meningitis | 0.5 | 156 | | 156 | | | |
| Sporotrichosis | 0.2 | 69 | 69 | | | | |
| Histoplasmosis | 0.0 | 8 | 8 | | | | |
| Total fungal burden | | **581,174** | **498,683** | **23,400** | **59,741** | **1,528** | **701** |

[a] Per 100,000 females

**RVVC** recurrent vulvovaginal candidiasis, **CPA** chronic pulmonary aspergillosis, **TB** tuberculosis, **ABPA** allergic bronchopulmonary aspergillosis, **SAFS** severe asthma with fungal sensitization, **PCP** Pneumocystis pneumonia

support) than Peru, where the size of these population at risk is still small. With African countries, the main difference is related to a larger population of HIV-infected persons not on ART compared to Peru, while Brazil has a larger numbers of transplant recipients and endemic mycosis.

We believe the 1.9% figure is an underestimation of the real burden of serious fungal diseases in Peru that could be explained by several reasons. First, mycotic diseases are underdiagnosed due to inadequate access to health services, the limited sensitivity of available diagnostic tests, and an inadequate level of clinical suspicion of fungal diseases explained by inadequate training of health personnel, a common problem across the world. These reasons could explain the small number of endemic mycosis diagnosed in Peru, even though one third of the territory has conditions for acquisition of them. In addition, the inadequacy of diagnostic capacity may explain the small number of PCP and CM in HIV-positive persons actually diagnosed.

Alternative explanations for the low number of histoplasmosis and paracoccidiodomicosis cases could be the low population density of the endemic areas, and the existence of effective immunity among residents of these areas. This later explanation is supported by the occurrence of histoplasmosis outbreaks among tourist visiting caves in these areas. The hyperendemic area of sporotrichosis is also an area of relatively low population density, and as consequence, the number of persons affected is relatively low.

The second reason for believing that we have an underestimated burden is that reporting of fungal diseases is not mandatory and there is no surveillance system for any mycotic disease. Third, the lack of good data to estimate the size of populations at risk drove us to use conservative figures, as we did with asthma patients, or to use figures generated from incomplete reporting, as could happen with HIV data.

This first estimation of the fungal burden in Peru needs to be refined though the use of improved measures of fungal diseases and of populations at risk. We acknowledge that by using data not always representative of the whole country and data not locally produced has the potential of introducing an important level of inaccuracy. Use of better data will produce better estimations. However, our results create awareness, pointing out fungal disease as a public health priority and highlight the need of surveillance, implementation of prevention strategies, training, access to diagnosis testing and research in mycotic diseases.

#### Compliance with ethical standards

**Potential conflicts of interest** Dr. Beatriz Bustamante currently receives funding for research from Merck Sharp & Dohme Corp (Merck Investigators Studies Program).

Dr. David W. Denning holds Founder shares in F2G Ltd a University of Manchester spin-out antifungal discovery company, in Novocyt which markets the Myconostica real-time molecular assays and has current grant support from the National Institute of Health Research, Medical Research

Council, Global Action Fund for Fungal Infections and the Fungal Infection Trust. He acts or has recently acted as a consultant to Astellas, Sigma Tau, Basilea, Scynexis, Cidara and Pulmocide. In the last 3 years, he has been paid for talks on behalf of Astellas, Dynamiker, Gilead, Merck and Pfizer. He is also a member of the Infectious Disease Society of America Aspergillosis Guidelines and European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines groups.

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