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Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Supplement article

Burden of serious fungal infections in Mexico

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Summary

Serious fungal infections (SFIs) could be more frequent than are recognised. Estimates of the incidence and prevalence of SFIs are essential in order to identify public health problems. We estimated the rates of SFIs in Mexico, following a methodology similar to that used in prior studies. We obtained information about the general population and populations at risk. A systematic literature search was undertaken to identify epidemiological reports of SFIs in Mexico. When Mexican reports were unavailable, we based our estimates on international literature. The most prevalent SFIs in Mexico are recurrent vulvovaginal candidiasis (5999 per 100 000) followed by allergic bronchopulmonary aspergillosis (60 per 100 000), chronic pulmonary aspergillosis (15.9 per 100 000), fungal keratitis (10.4 per 100 000), invasive candidiasis (8.6 per 100 000) and SFIs in HIV (8.2 per 100 000); coccidioidomycosis (7.6 per 100 000), IA (4.56 per 100 000). These correspond to 2 749 159 people affected in any year (2.45% of the population), probably >10 000 deaths and 7000 blind eyes. SFIs affect immunocompromised and healthy populations. Most are associated with high morbidity and mortality rates. Validation of these estimates with epidemiological studies is required. The burdens indicate that an urgent need to improve medical skills, surveillance, diagnosis, and management of SFIs exists.

Key words: Epidemiology, fungal infection, Mexico, aspergillosis, burden.

Introduction

Candidaemia is one of the most studied invasive fungal infections (IFIs), with a major impact on survival.[1] However, many other serious fungal infections (SFIs), also associated with higher comorbidity and mortality, have been relatively neglected by both medical and scientific communities as well as more generally. In Mexico an extensive range of SFIs occur as opportunistic infections in immunocompromised or critically ill patients, pulmonary diseases in those with underlying pulmonary problems and injury related infections affecting healthy people. Also, Mexico has the widest diversity of endemic mycoses as well as both rural developing and urban developed populations. This is a perfect storm for fungal disease.

Estimates of the incidence and prevalence of SFIs are essential in order to identify and highlight the public health problems and priorities. Recently estimates of the rates of SFIs have been made in ~50 countries including Spain,[2] India,[3] Nigeria[4] and Ireland.[5]

No attempt has been made to estimate the total burden of fungal infections in Mexico. We attempted this, following a similar methodology as used in prior studies, mostly by identifying rates in underlying populations at risk.

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Methods

To estimate the burden of SFIs, first, it was necessary to define the general Mexican population and potential populations at risk. This information was obtained from the World Health Organization [6] and Pan-American Health Organization [7] (WHO and PAHO) annual reports and the INEGI (Mexican Institute of Statistics and Geography).[8] The total and female Mexican populations estimates were obtained from the INEGI report of 2010.[8] The populations at risk needed to calculate the burden of SFIs were individuals living with chronic obstructive pulmonary disease (COPD), asthma, human immunodeficiency virus (HIV), pulmonary tuberculosis with and without cavities, leukaemia, transplant of solid organ and haematopoietic stem cell recipients (HSCT).

Human immunodeficiency virus and tuberculosis population estimates were obtained from the WHO reports.[9] Chronic obstructive pulmonary disease prevalence was obtained from various reports; from the National Respiratory Diseases Institute (INER) during 2002,[10] the proportion of patients with COPD GOLD III/IV were obtained from the WHO reports and systematic review in Latin America.[9,11] Tuberculosis rates were taken from the World Health Statistics published by WHO in 2013.[9] In addition the asthma prevalence in Mexico was found in the World Health Survey reports.[12.]

Leukaemia and HSCT rates in Mexico were obtained from the GLOBOCAN project website and LABMT (Latin-American network for Blood & Marrow Transplantation) [13,14]. The CENATRA (Mexican National Center for Transplants) provided the statistics of transplant of solid organs in Mexico.[15]

The SFIs analysed were allergic bronchopulmonary aspergillosis (ABPA), severe asthma with fungal sensitisation (SAFS), invasive aspergillosis (IA), *Pneumocystis* pneumonia (PCP), cryptococcosis and cryptococcal meningitis, fungal keratitis, candidaemia, chronic pulmonary aspergillosis (CPA), mucormycosis, recurrent vulvovaginal candidiasis (rVVC), histoplasmosis and coccidioidomycosis. Multiple literature searches were undertaken to identify all the epidemiology reports detailing fungal infections in Mexico. When reports of the fungal infections of interest were unavailable to inform our estimates, we based our calculations on rates of SFIs reported in the international literature.

Allergic bronchopulmonary aspergillosis and SAFS are diseases associated with an exaggerated allergic response to fungal allergens with infectious and non-infectious complications. The prevalence rates of ABPA complicating asthma, CPA after tuberculosis (TB) cavity and CPA complicating other diseases were calculated, using the prior estimates of Denning *et al.*, as shown in Table 1.[16,17] These estimates were made assuming an ABPA prevalence rate of 2.5% in asthma and 22% in survivors of pulmonary TB with a cavity and 2% in those without a cavity, in order to calculate the prevalence rate over a period of 5 years.[16,17]

In the study performed by Guinea *et al.* [18] the prevalence of IA documented among the individuals with COPD admitted to hospital was 1.3%.

Burden of IFIs and IA in leukaemia, HSCT and solid organ transplant (SOT) were calculated based on a prospective cohort study from the USA (TRANSNET), and on several prior retrospective reports from Italy and Brazil,[19–22] see Table 1.

The burden of fungal keratitis was calculated using the prevalence rate of infectious keratitis (0.148%) and infectious keratitis leading to corneal blindness in at least one eye (0.091%) as detailed by Cao *et al.* [23]. In addition, to calculate the burden of fungal keratitis in México (7% of the infectious keratitis), we used the 20-years report of Vanzzini-Zago *et al.* that was performed in a Mexican national ophthalmology institute.[24] The estimated candidaemia incidence was based on prior reports of population-based surveys,[25] Table 1. For mucormycosis, we used a rate of 0.9–1.2 cases per million reported previously.[26]

Vulvovaginal candidiasis affects 70–75% of women at least once during their lives, mainly during childbearing age. Recurrent VVC (defined as four or more episodes every year) affects 5–9% of adult women in their fertile years; a 6% rate was used to calculate the annual rate of recurrent VVC.[27] Episodes occurring after the menopause were ignored.

The proportion of PCP, histoplasmosis and cryptococcal meningitis in advanced-HIV infection were obtained from Mexican clinical and autopsy series reporting opportunistic infections among HIV patients prior to 2002.[28] The prevalence of PCP was reported in these series between 18.6% and 30%,[28] so we set a 24% median rate for calculation purposes. Meningeal cryptococcosis was reported in 3–20% of the advanced-AIDS patients and 11% was set as the median rate for the estimates. Finally, histoplasmosis was reported between 3.7% and 13% in AIDS and we used 8% as the median rate.[28]

Table 1 Prevalence rates previously reported, used to calculate the burden of serious fungal infections.

Disease	Prevalence (%)	Disease	Prevalence (%)
ABPA	2.5	PCP in HIV[1]	24
SAFS	35 of severe asthma individuals	Cryptococcal meningitis in HIV[1]	2.8–20
IA in COPD	1.3	Histoplasmosis in HIV[1]	3.7–12.7
SFIs in leukaemia	4.6–18.7	Fungal keratitis[1]	7 (6.1–7.9)
IA leukaemia	2.6–13.4	Non fungal infectious keratitis	0.148
SFIs in HSCT	3.4–11.3	Infectious keratitis leading corneal blindness at least in one eye	0.091
IA in HSCT	1.6–2.3	Tuberculosis cavity in México[1]	35
IFIs in renal, heart and liver transplant	1.3–4.7	CPA in TB cavity (5-year estimated prevalence rate)	22
IA in liver, heart and renal transplant	0.7	Annual CPA after TB rate	9
Candidaemia	0.005	VVC lifetime risk	70–75
Mucormycosis	1.2 cases per million	rVVC	6

ABPA, allergic bronchopulmonary aspergillosis; IA, invasive aspergillosis; COPD, chronic obstructive pulmonary disease; TB, tuberculosis; CPA, chronic pulmonary aspergillosis; IFIs, invasive fungal infections; HSCT, hematopoietic stem cell transplant; VVC, vulvovaginal candidiasis; rVVC, recurrent vulvovaginal candidiasis; SAFS, severe asthma with fungal sensitisation; SFIs, serious fungal infections; PCP, *Pneumocystis* pneumonia. IFIs – refers to opportunistic fungal infections such as invasive aspergillosis, invasive candidiasis, fusariosis and scedosporiosis.

[1]Data collected from Mexican resources.

Coccidioidomycosis and histoplasmosis are both major endemic mycoses in Mexico. However, since 1995, the epidemiology of coccidioidomycosis and histoplasmosis in Mexico has not been reported.[29] The most recent data about the annual rate of histoplasmosis in the general population comes from reports of epidemic forms of histoplasmosis prior to 1997 and ranges between 0.1–0.29 cases per 100 000. In addition, information reported in the 50s and 60s exists about the exposure to *Histoplasma* is based on positive skin testing and ranged between 5–50%.[30] Therefore, the impact of HIV on the rate of histoplasmosis has not been defined at all. For coccidioidomycosis, two estimates were made in this study. The first estimate was the burden of exposure measured by positive coccidioidin skin testing. The positive skin test in the endemic states range from 10% to 90%, see Fig. 1. Mexico and USA share a common frontier; California, Nevada, Arizona and New Mexico share borders with Coahuila, Chihuahua, Sonora, Nuevo León, Tamaulipas and Baja California Norte. These zones are geographically similar in climate and soil conditions.[31] Based on the geographical similarities, we made the second estimate for burden of infection, in these Mexican states, assuming the rate of coccidioidomycosis occurrence to be 43/100 000 in California, Nevada, Arizona and New Mexico reported in 2013.[32]

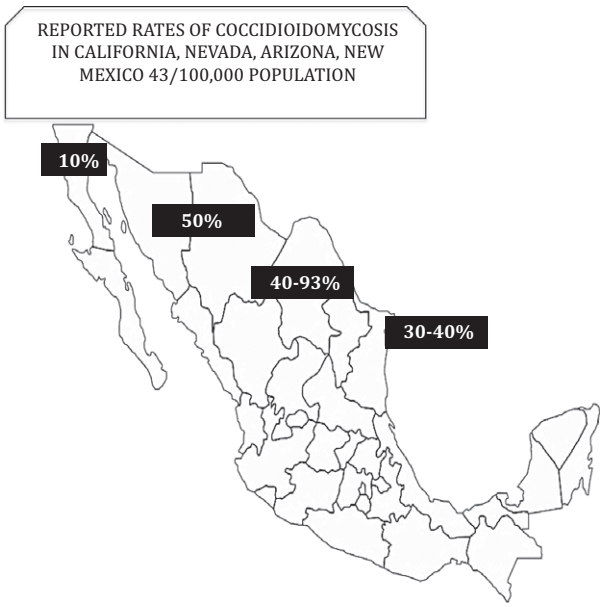

Figure 1 Positive skin test rates for coccidioidomycosis and reported rates of infection in endemic zones of the US.

Results and discussion

Country population

The last country census in Mexico was collected during 2010 and according to this census, the Mexican population was 112 336 538 individuals with a Gross Domestic Product (GDP) of 10 307 USD per person in 2013.[8] Adults comprised 71% of the population, and Mexican female of age >15 years was 39% of the total population (Table 2).[8] The crude prevalence of COPD estimated by the INER in the PLATINO study during 2002 was 7.8% (CI 95%: 5.9–9.7%) representing an equivalent of 3.8 million individuals greater than the 30-year-old population in Mexico.[10] Severe infections (including IA) are more commonly seen among subjects with GOLD III/IV (0.7/0.2% of the general population).[11] Therefore, we calculated the burden of severe COPD among the general population of around 346 984 individuals. The burden of asthma in the adult population was about 1.9 million, assuming a prevalence rate of asthma to be 2.4%.[12] The HIV population (during 2013) was calculated to be 175 245 persons (156 per 100 000), according to the WHO, 80% of the individuals with HIV in Mexico receive antiretroviral therapy (ART).[9] We used the proportion of individuals not receiving ART according to the WHO 2010 guidelines (i.e. CD4 cell count $<350 \times 106\ l^{-1}$) and proportion of late diagnosis to make a better estimate of SFIs in this group of individuals.[33] The estimated burden for tuberculosis was 29 207 cases during 2013 based on a prevalence rate of 26 per 100 000 as reported by the WHO [6], 55% ($n = 16\ 080$) for pulmonary TB,[6] see Table 2. Estimated burden for leukaemia, solid transplant and HSCT estimates are also shown in Table 2.

Burden of serious fungal infections (SFIs)

The most prevalent SFI in Mexico is recurrent VVC (5999 cases per 100 000) followed by ABPA (60 per 100 000), CPA (15.9 per 100 000), fungal keratitis (10.4 per 100 000), invasive candidiasis (8.6 per 100 000), SFIs in HIV (8.2 per 100 000), coccidioidomycosis (5.3 per 100 000) and IA (4.56 per 100 000). All these SFIs correspond to a total burden of 2 749 159 people affected in any year (2.45% of the population), with probably far greater than 10 000 deaths and 7000 blind eyes (Table 3).

Table 2 Populations and rates required to calculate burden of serious fungal infections in mexico.[2]

Population	Number	Prevalence and annual rates
Total Mexican population in 2010	112 336 538	
Total adult population in 2010 (>15 years old)	79 758 941	71%
Mexican female >15 years old population in 2010	43 979 596	39%
COPD 2002 (persons >30 years old)	3 855 389	7.8% (5.9–9.7)
COPD GOLD III/IV (2002, 2014)	269 877/77 107	0.7%/0.2%
Asthma 2014	1 914 214	2.4%
Severe Asthma	191 421	10%
HIV population 2013	175 245	156/100 000 $year^{-1}$
HIV population late testers	106 899	95/100 000 $year^{-1}$
HIV population not receiving ART	21 375	19/100 000 $year^{-1}$
Tuberculosis 2013[1] (all forms)	29 207	26/100 000 $year^{-1}$
Pulmonary tuberculosis[1]	16 080	14/100 000 $year^{-1}$
Leukemia 2012	6325	5.6/100 000 $year^{-1}$
Renal transplant recipients 2013	2707	2.4/100 000 $year^{-1}$
HSCT recipients 2010	11–560	0.01–0.49/100 000 $year^{-1}$
HSCT recipients 2012	382	0.34/100 000 $year^{-1}$
Allogenic-HSCT 2012	200	0.18/100 000 $year^{-1}$
Liver transplant recipients 2013	149	0.13/100 000 $year^{-1}$
Heart transplant recipients 2013	44	0.04/100 000 $year^{-1}$

COPD, chronic obstructive pulmonary disease; HSCT, hematopoietic stem cell transplant; ART, antiretroviral therapy.

[1]Tuberculosis (including population con HIV and without HIV and TB).

[2]The data in this table came from local or international organisations made for Mexican population.

Table 3 The top 10 of serious fungal infections in Mexico.

Serious fungal infection	Burden	Rate per 100 k	Mortality rate[3](%)
rVVC	2 638 755	5999[1]	0
ABPA	47 855	60[2]	<1
CPA	18 246	15.9	14–24
Fungal keratitis	11 638	10.4	<1
Invasive candidiasis	9646	8.6	46–75
SFIs in HIV	9191	8.2	20–80
Coccidioidomycosis	8552	7.6	<1–70
IA COPD	4510	4.0	36–58
SFIs in leukaemia	632	0.56	30–95
Mucormycosis	134	0.1	30–90
Total	2 749 159	2447	

ABPA, allergic bronchopulmonary aspergillosis; IA, invasive aspergillosis; COPD, chronic obstructive pulmonary disease; CPA, chronic pulmonary aspergillosis; rVVC, recurrent vulvovaginal candidiasis; SFIs, serious fungal infections.

[1]Rated taking the population of Mexican women of age >15 years.

[2]Rate taking in count adult Mexican population of age >15 years.

[3]References 1,17,18

Recurrent VVC (rVVC)

In the population of Mexican women of age >15 years, we estimated that at least 2.5 million women have four or more episodes of rVVC each year, Table 4. rVVC has been associated with depression and anxiety in at least 50% of these women, it also represents at least 33 work hours lost per year and associated costs ranged from €266 $year^{-1}$ to €1130 $year^{-1}$.[34] These findings help to highlight the impact of rVVC on the daily lives among these Mexican women and need for more effective ways to manage them.

ABPA, SAFS and CPA after TB cavity

Allergic bronchopulmonary aspergillosis is characterised by exacerbations of asthma associated with recurrent transient chest radiographic infiltrates, bronchiectasis and peripheral and pulmonary eosinophilia.[35] Such exacerbations and poor asthma control lead to greater rates of hospital admissions, costs and morbidity rates.

According to prior reports of Denning *et al.* [17], we estimated that ABPA affects 2.5% of the individuals with asthma in Mexico and therefore, its estimated prevalence rate among the general population is 60 cases per 100 000 individuals, with 47 855 patients affected. A related disorder, which partially overlaps with ABPA, is SAFS, see Table 1. As in other country estimates, if the rate of severe asthma in adults is 10% of the total burden of asthma and 35% of these patients are sensitised to fungi, the

Table 4 Estimated affected individuals with serious fungal infections.

Fungal infection	Burden	Rate per 100 000[1]
rVVC (rate per 100 000 women)	2 638 755	5999
ABPA among asthma individuals	47 855	60
IA in COPD[2]	4510	4.0
Fungal keratitis	11 638	10.4
Fungal keratitis causing blindness	7155	6.4
SFIs in HIV		
PCP in HIV	5130	4.5
Histoplasmosis in HIV	1710	1.5
Cryptococcosis in HIV	2351	3.4
Invasive candidiasis	9646	8.6
Candidaemia	5617	5
Candida peritonitis	5596	4.98
Candida peritonitis without candidaemia	4029	3.6
Total prevalence of CPA	18 246	15.9
Annual CPA after TB	1447	1.1
5 years period prevalence	4562	4
SFIs in leukaemia	632	0.56
IA in leukaemia	506	0.45
Endemic SFIs		
Coccidioidomycosis	8552	7.6
Histoplasmosis general population (estimates based in outbreaks)	112–325	0.1–0.29
Mucormycosis	134	0.12
IFIs in renal, liver and heart transplant recipients	44	0.04
IA in renal, heart and liver transplant recipients	20	0.017
IFIs in allogenic-HSCT	14	0.013
IA in allogenic-HSCT	4	0.0036

ABPA, allergic bronchopulmonary aspergillosis; IA, invasive aspergillosis; COPD, chronic obstructive pulmonary disease; TB, tuberculosis; CPA, chronic pulmonary aspergillosis; IFIs, invasive fungal infections; HSCT, hematopoietic stem cell transplant; VVC, vulvovaginal candidiasis; rVVC, recurrent vulvovaginal candidiasis; SFIs, serious fungal infections; PCP, *Pneumocystis* pneumonia.

[1]Rate per 100 000 total Mexican population in 2010 – 112 336 538 except for the rate of rVVC based on the population of Mexican women of age >15 years (n = 43 979 596) and ABPA based on adult Mexican population.

[2]IA in COPD was calculated just for COPD individuals with GOLD III/IV, as 100% of IA in this population has been documented among these groups.

SAFS prevalence is 66 997.[3] Double counting is possible, as some ABPA patients have severe asthma and some SAFS patients are sensitised to *Aspergillus fumigatus*. Finally, ABPA is a TH2 hypersensitivity lung disease caused by bronchial colonisation with species of *Aspergillus.*[35] However, other fungi such as *Penicillium, Curvularia, Alternaria* and *Cladosporium* are occasionally responsible for similar syndrome,[35] therefore, the allergic bronchopulmonary mycosis rate could be higher.

During 2013 in Mexico, 16 080 cases of pulmonary tuberculosis were reported. We assumed that approximately 35% of TB individuals have a residual cavity (n = 5628).[16] Therefore, 22% of these and 2% of those without a cavity (n = 1447) could have CPA in a TB cavity (total CPA incidence following PTB at 1 year).[16] The 5-year prevalence, assuming an annual mortality or surgical resection rate of 15%, would mean that nationally 4562 patients are affected (4 per 100 000).

Chronic pulmonary aspergillosis also complicates ABPA, sarcoidosis, those with non-tuberculous mycobacterial infection, lung surgery, pneumothorax and COPD. Therefore, it is likely that TB is the underlying diagnosis in only under 25% of patients.[36] If true, studies need to be done to establish this, the total prevalence of CPA in Mexico is estimated at 15.9 per 100 000 among individuals with all underlying diagnoses, is 18 246 cases per year. CPA is one of the most severe or the most severe complication after tuberculosis and requires antifungal therapy and/or thoracic surgery to reduce both morbidity (associated with loss of lung function and damage) and mortality. The mortality after surgery is lower in aspergilloma but much higher in more complex, multicavity diseases; therefore, careful risk evaluation is required.[16,37]

Fungal keratitis

The global estimation of visually impaired and blind people in 2010 was about 285 million (4.3% prevalence) and 39 million (0.58% prevalence) respectively.[38] In Latin America, the prevalence rates have been reported to be even higher.[39] Corneal ulceration is an underrecognised and leading cause of unilateral visual loss, mainly due to infectious keratitis.[40] In Mexico, estimation of the burden of infectious keratitis was calculated using a prevalence rate of 0.148% as reported in China by Cao *et al.*, resulting in 166 258 cases.[23] Taking the burden of infectious keratitis estimated for Mexico (n = 166 258) into account, we estimated the prevalence of fungal keratitis from a previous report in Mexico where it was found that 7% of the infectious keratitis cases were due to fungi.[24] Therefore, the burden of fungal keratitis in Mexico was estimated to be 11 638 cases leading to blindness in at least one eye in 61% (n = 7099) of these individuals (Table 4).[23] As fungal culture is insensitive and fungi are difficult to identify by microscopy, this could be significant underestimation of the size of the problem. The WHO has declared visual impairment and blindness as a significant public health problem and it has developed the Global Eye Health Action plan to reduce avoidable visual impairment. In order to set policies and priorities, monitoring the magnitude of visual impairment is essential for developing prevention and elimination programs.[38]

SFIs in HIV

Pneumocystis pneumonia, histoplasmosis and cryptococcal meningitis are the most common life-threatening SFIs in HIV. For calculation purposes, we set the overall prevalence of PCP at 24%, central nervous system cryptococcosis at 11% and histoplasmosis at 8%, consistent with Mexican clinical and autopsy series published prior to 2002.[28]

The prevalence of HIV in Mexico is 156 cases per 100 000 and therefore, the overall estimate is 175 245 persons.[9] In a Mexican study, it has been reported that 61% (N = 106 899) of hiv-infected individuals present late (CD4 cell count $<200 \times 10^6$ l^{-1})[33] and the proportion of ART therapy in this group is 80%,[9] this indicates that 21 379 advanced-HIV individuals are at risk of opportunistic infection. Assuming this, the prevalence of PCP would be 5130 cases, cryptococcosis 2351 and histoplasmosis 1710 cases annually.

On the other hand, the estimated incidence rate of HIV is four cases per 100 000 inhabitants[41] each year meaning 4493 new HIV cases are expected each year, and 61% of these (n = 2740) are diagnosed late.[33] Using this alternative approach, new cases of PCP, cryptococcosis and histoplasmosis per year could be 657 301 and 219 respectively.

It is most likely that the incidence of these fungal infections has decreased with the increasing availability of ART; however the proportion of late diagnosis is still high. Other Latin-American studies after 2005 based on autopsy series still report a frequency of PCP >15%, which means a good proportion of individuals are not diagnosed during life.[42] Increasing the medical mycology diagnostic capabilities and skills in hospital

laboratories is likely to decrease the mortality rate as was shown by Adenis *et al.* in decreasing the early mortality due to histoplasmosis in Guiana.[43]

Endemic fungal infections (EFIs)

In Mexico EFIs are not noticeable and so accurate estimations of infection are problematic. The most recent studies in Mexico that evaluated the prevalence, measured by positive skin testing (exposure), were reported prior to 1995. Studies reporting prevalence and incidence have not been performed in Mexico. In addition to the non-reportable nature of these diseases, the lack of diagnostic tool availability across the county limits the recognition of these infections.

We estimated the burden of two main EFIs in Mexico, histoplasmosis and coccidioidomycosis. In addition, sporotrichosis is the second most frequently reported subcutaneous mycosis after eumycetomas, and the areas where the reports come more often are humid, tropical and central Mexican states such as Michoacan, Jalisco, Veracruz, Guerrero, Puebla and Guanajuato.[30,44,45] Puebla and Jalisco are known to be hyperendemic for sporotrichosis and prevalence of exposure as measured using skin test with sporotrichin is approximately 2.5 cases per 1000 inhabitants (approximately $n = 3282$). The incidence of acute cases is unknown.[44] There are no burden data on chromoblastomycosis, eumycetoma and paracoccidioidomycosis.

Histoplasmosis among general population

Based on prior reports of skin test surveys for histoplasmosis, the estimated population exposure in the entire country is about 11 233 653–56 168 269. The annual rates of histoplasmosis reported in Mexico between 1988 and 1994 in the general population range from 0.1–0.29/100 000[46] (these rates only reflect the so called 'epidemic form of histoplasmosis' meaning the acute pulmonary and disseminated forms) and the annual burden estimates based on these data were 112–325 cases. We thought that this estimate is a very substantial underestimation as it is not derived from a surveillance program. In addition, the diagnostic methodologies during 1988 and 1994 were diverse. Histoplasmosis has been reported to occur mainly in the central and south-eastern parts of Mexico (Veracruz, Oaxaca, Campeche, Tabasco and Chiapas),[30] which are the poorest areas and the diagnosis is generally lacking.

Coccidioidomycosis

In contrast to histoplasmosis, coccidioidomycosis is suspected to be an endemic in the arid northern regions of Mexico. These arid zones include the Mexican states: Coahuila, Chihuahua, Sonora, Tamaulipas, Nuevo León and Baja California that constitute the frontier with USA and its 'Cocci' endemic zones.[29] In Mexico, the last estimations of *Coccidioides* exposure were made prior to 1970, using skin testing (coccidioidin).[29] Using these background data and other regional reports[29] describing a general increase in the skin testing positivity rates reported during the 90s, we estimate the total burden of exposure in the suspected endemic states, to be between six and eight million (Table 5).

We used the rates of infection published by CDC in 2013[32] to calculate the rates of infection in the Mexican states bordering the endemic states in USA (California, Nevada, Arizona and New Mexico). We estimated the burden to be about 8552 new cases per year (incidence 7.6/100 000 population), see Fig. 1 and Table 5). Symptomatic patients typically experience a self-limited influenza-like illness, but some develop severe or chronic pulmonary disease, although only <1% of the patients develop disseminated disease.[32] Assuming this, 85 cases of disseminated disease, including coccidioidal meningitis are expected each year Coccidioidomycosis can be costly and debilitating, with nearly 75% of the patients missing work or school because of their illness and more than 40%

Table 5 Exposure and infection due to coccidioidomycosis.

State	Total population	Exposure based on PST rate (%)	Estimated exposure burden	Estimates of infection[1]
Coahuila	2 748 391	40–93	1 099 356–2 556 003	1181
Chihuahua	3 406 465	At least 50	1 703 232	1464
Sonora	2 662 480	At least 50	1 331 240	1144
Nuevo León	4 653 458	30–40	1 396 037–1 861 383	2000
Tamaulipas	3 268 554	10–30	326 855–980 566	1405
Baja California	3 159 070	10	315 907	1358

[1]Based on US endemic areas (43 per 100 000 population).

requiring hospitalisation.[32] Due to the high morbidity rate associated with these diseases, the authors consider that a national survey should be set up, followed by the ongoing surveillance program, for these neglected conditions.

Candidaemia and invasive candidiasis

Invasive candidiasis is one of the most studied IFIs, its incidence has increased in recent years and the related mortality usually exceeds >30%.[1] Thanks to this focus, more information about candidaemia is available. For this study, the estimated burden of candidaemia was made using prior reports of population-based surveys. The annual rates of candidaemia as reported by Arendrup, range between 1.2 and 14 cases per 100 000 inhabitants.[25] A conservative estimation of five case per 100 000 inhabitants was used and the estimated burden for Mexico was 5617 cases per year. Almost all the cases of candidaemia occur in the hospital context, and within this setting, ICU incidence of candidaemia is 10-fold higher than non-ICU incidence.[25,47] In a recent Mexican report from two tertiary care centres[48] this proportion was very similar in ICU settings, 17 cases per 1000 admissions, and non-ICU settings, two cases per 1000 admissions. Notably, 31% of the ICU candidaemia cases had concomitant abdominal surgery in this Mexican report.[48] This suggests that at least 5056 (90%) cases of candidaemia in our estimate occur in ICU, and 1567 cases (31% according with the Mexican report) could be associated with abdominal procedures and therefore, could represent *Candida* peritonitis with concomitant candidaemia.

Montravers *et al.* reported that a 28% of individuals with *Candida* peritonitis have concomitant candidaemia.[49] If we take the assumption of Montravers, our 1567 cases represent the 28% and therefore, there will be 4029 cases of *Candida* peritonitis without candidaemia. Thus, the total number of *Candida* peritonitis cases estimated would be very similar to the candidaemia estimation (5596 cases, 4.98 cases per 100 000 inhabitants).

Candidaemia is the most frequent clinical manifestation of invasive candidiasis; other manifestations are *Candida* peritonitis/abdominal sepsis, meningitis, osteomyelitis, and chronic or acute disseminated candidiasis.[50] These non-candidaemic manifestations are difficult to diagnose. Taking into account the rates of candidaemia and *Candida* peritonitis without candidaemia, we can conclude that the incidence rate of invasive candidiasis is probably higher than 8.6 cases per 100 000 inhabitants and at least 3.5 per 100 000 inhabitants die each year due to this condition, many without a diagnosis or adequate treatment.

Mucormycosis

Mucormycosis is a less frequent SFI compared with candidaemia, cryptococcosis and aspergillosis, but has attracted the attention of several researchers due to its increasing occurrence among immunosuppressed individuals, mainly leukaemic patients. Other affected populations are diabetic and traumatic individuals.[51,52]

Bitar *et al.* reported a population-based study for zygomycosis incidence in France. This incidence ranged from 0.7 per million in 1997 to 1.2 in 2006.[26] Based on this report, we estimated the burden to be 134 cases assuming a higher rate of 1.2 cases per million. We choose the higher rate because we think in Mexico the incidence of mucormycosis could be increasing given the increasing haematological malignancy and diabetes. Over 60% of mucormycosis cases in Mexico are in diabetics.[53,54] Diabetes, in Mexico, has increased 59% from 2000 to 2012 and, only 25% of these have good glycaemic control.[55]

Invasive aspergillosis

IA in COPD

Chronic obstructive pulmonary disease has emerged as a significant risk factor for invasive aspergillosis.[1] The risk is associated with ciliary activity impairment, immunosuppression due to steroids use (inhaled or systemic) and a broad-spectrum of antibiotics mainly during ICU-hospitalisation due to exacerbations.[18,56]

The burden of IA in COPD individuals was estimated based on the population with GOLD III/IV score (n = 346 984 see Table 2). We used the incidence rate of IA in COPD reported by Guinea *et al.* (1.3% of COPD individuals developing IA each year), which was observed among population with GOLD III/IV score,[18] and not the higher rate reported from China, 3.9%.[56] Assuming this, the annual estimated number of IA cases in COPD in Mexico is 4510 and at least 36% (n = 1623) to 58% (n = 2616) of these will not survive or receive antifungal management (Table 3).[18,55,56]

SFIs in hematologic conditions

The prevalence of SFIs found in this group of individuals ranges from 4.6% to 18.7%.[19,22] The prevalence of IA ranged from 2.6% to 13.4%. We set the average prevalence of SFIs at 10% and for IA at 8%.[19,22] The estimated burden using these rates was 632 cases of

SFI per year, mainly due to IA (506 cases of IA per year) assuming 6325 cases of leukaemia per year (Tables 2 and 4).[13]

Similar to the estimate of SFIs and IA for leukaemia, we used an average prevalence of 7% and 2% respectively to estimate the burden among allogeneic-HSCT recipients based on rates reported in the TRANSNET studies and by Nucci *et al.* [21,22]. In Mexico the number of total HSCT performed per year ranged from one to 49 per 10 million, also during 2012, the LABMT reported 200 allogeneic-HSCTs performed in Mexico.[14] Taking in count these reports we estimated 14 cases of SFIs per year among this population, four of them due to IA.

SFIs in solid organ transplant, IA in solid organ transplant

The burden of SFIs among solid organ transplants was estimated using the statistics reported in the TRANSNET study.[20] In Mexico the SOT procedures most frequently performed are kidney, liver and heart.[15] In Mexico during 2013, 2707 renal transplants, 149 liver transplants and 44 heart transplants were performed corresponding to 10 times less transplants than countries such as USA,[50] (Table 2). The incidence rate of SFIs considered from the TRANSNET report were 1.3% for kidney, 3.4% for heart and 4.7% for liver; and in all cases, we considered the incidence rate of IA to be 0.7%.[20] The total burden of SFIs for these three types of SOT was 44 cases, and IA accounted for 20 of these. This is probably an underestimation as only confirmed cases were included in the TRANSNET.

Conclusions

Mexico has a large partly rural, but mostly urban population, a diverse climate and geomorphology and wide range of health facilities. It has modest HIV and TB burdens, but a large endemic mycosis burden, notably with coccidioidomycosis and histoplasmosis. SFIs are a group of diseases causing high morbidity and mortality rates. The diversity of SFIs is great (over two million cases), with substantial numbers of likely deaths (>10 000) each year in the context of critical care, leukaemia therapy, AIDS and after tuberculosis. In addition, over 7000 blind eyes are likely caused by fungal keratitis each year. In addition, complications following SFIs imply lifelong disabilities, work hours lost and high rates of hospitalisation. Many diverse populations in Mexico are affected, primarily due to the distinct geographical distribution of endemic mycoses and specific risk groups for opportunistic fungal infections.

The estimates are, in general, conservative and the lack of high quality epidemiological data from Mexico is an important limitation for this report. Surveillance of fungal infections requires more development and is likely to demonstrate higher numbers than our estimates. Many estimates were derived from rates reported from other countries, despite obvious differences with Mexico in their ecologic, genetic, cultural and economic backgrounds. However, these estimates help to give a general overview of the likely disease burden and hopefully give impetus for the performance of local surveillance.

Our estimations are indicative that there is an urgent need to provide appropriate medical skills, surveillance, diagnostic resources, and management strategies for SFIs in Mexico. A first step could be the mandatory notification of endemic mycosis to health authorities, systematic surveillance of IFIs among populations at risk such as HIV, leukaemia, COPD, asthma and transplant and promote formal training in medical mycology. Improvement to improve the diagnosis and management skills mainly in those SFIs with high mortality rate (invasive candidiasis, cryptococcosis, aspergillosis and histoplasmosis) and high disability rate (fungal keratitis, coccidioidomycosis) is required.

Conflict of interests

DECL has been paid for talks on behalf of Pfizer, is member of the Mexican Society of Infectious Diseases and Clinical Microbiology, and the Mexican Society of Mycology. DAJ has received research funding from Pfizer and Gilead, and acts as a consultant to Pulmocide Ltd. DWD or Dr 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 a current grant support from the National Institute of Allergy and Infectious Diseases, the National Institute of Health Research, NorthWest Lung Centre Charity, Medical Research Council, Astellas and Fungal Infection Trust. He acts as a consultant to the Trinity group, T2 Biosystems, GSK, Sigma Tau, Oxon Epidemiology and Pulmicort. In the last 3 years, he has been paid for talks on behalf of Astellas, 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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