mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Supplement article

Burden of fungal infections in Qatar

Saad J. Taj-Aldeen,[1] Prem Chandra[2] and David W. Denning[3]

[1]*Mycology Unit, Microbiology Division, Department of Laboratory Medicine and Pathology, Doha, Qatar,* [2]*Medical Research Department, Hamad Medical Corporation, Doha, Qatar and* [3]*Manchester Academic Health Science Centre, The National Aspergillosis Centre, University Hospital of South Manchester, The University of Manchester, Manchester, UK*

Summary

Few estimates of fungal disease frequency have been attempted in the Middle East. We have estimated the burden of fungal infections in Qatar. The aim of the study was to compute and determine the burden of serious fungal infections, in an attempt to estimate fungal disease frequency, which has not previously been attempted in this country. Disease statistics were collected from the Microbiology laboratory database and from 2011 WHO statistics. The data are expressed per 100 000 populations. The reported cases of candidaemia rose to 288 with an estimated rate of 15.4/100 000. A real increase in the burden of candidaemia was found over that previously reported (12.9/100 000) for the years 2004–2009. *Candida* peritonitis was estimated in 8.02 cases/100 000 population. Recurrent ($\geq$4 year^{-1}) vaginal infections affect at least 32 782 women with a rate of 3506/100 000 inhabitants. Severe asthma with fungal sensitisation affected 1486 people, allergic bronchopulmonary aspergillosis 1126 people and chronic pulmonary aspergillosis 176 people. Rhinosinusitis, mucormycosis and *Fusarium* infection occurred at rates of 2.31, 1.23, 1.86 cases/100 000 respectively. The estimated rate of invasive aspergillosis was very low (0.6/100 000). Low rates of *Cryptococcus* meningitis and *Pneumocystis* pneumonia are attributable to low HIV infection rates. In conclusion, fungal infections are increasingly reported, especially candidaemia. Surveillance and guidelines are needed to optimise care and management of common fungal infections. In addition, a fungal registry system needs development for surveillance.

Key words: Burden of fungal infections, aspergillosis, candidiasis, mucormycosis, *Cryptococcus* meningitis, *Pneumocystis* pneumonia.

Introduction

Fungal infections are a significant and increasing public health problem worldwide, especially severely immunocompromised patients are at risk, those hospitalised with serious underlying diseases, such as those with HIV infection, haemato-oncological malignancies, recipients of immunosuppressive therapies, solid-organ or bone marrow transplant recipients and low-birthweight infants.[1–5] The incidence of fungaemia is growing and has dramatically increased within the past two decades. Such infections have been attributed to the common practice of prolonged hospitalisation of highly susceptible patients receiving advanced medical treatment; such conditions render patients more susceptible to invasive fungal infections.[6,7] The populations of patients at risk have expanded to include those with usually multiple underlying medical conditions, such as diabetes mellitus and those receiving some

Correspondence: Saad J. Taj-Aldeen, Mycology Unit, Microbiology Division, Department of Laboratory Medicine and Pathology, Hamad Medical Corporation, P.O. Box 3050, Doha, Qatar.
Tel.: +974 55050342. Fax: +974 44391813.
E-mail: saadtaj51@gmail.com

In association with the LIFE program at www.LIFE-Worldwide.org.

Submitted for publication 10 April 2015
Revised 15 May 2015
Accepted for publication 20 May 2015

doi:10.1111/myc.12386

monoclonal antibody therapies. Most serious infections are caused by *Aspergillus*, *Candida*, *Cryptococcus* and zygomycetes. Some opportunistic mycoses due to emerging fungal pathogens such as *Fusarium* among immunocompromised patients have been increasing[8,9] as well as uncommon yeast infections,[10] which are increasingly reported worldwide. Irrespective of the immune status of the patient, *Aspergillus* may develop severe osteomyelitis and post-operative infections after surgery due to poor air control in operating rooms[11] or immunosuppression treatment.[12]

In Qatar, the population is extremely mixed with many mobile workers from high-risk areas of the world particularly South East Asia. The average population of Qatar during the study period was 1 870 000 million. Several studies documenting fungal disease in Qatar are published. Mucormycosis cases were published in organ transplant, and haematological malignancy patients.[13–15] Bloodstream *Candida* infections were reported in paediatrics and adult patients.[6,10,16] Studies on *Aspergillus*[17,18] and *Pneumocystis* pneumonia[19,20] infections are limited to few cases. Asthma is the most common chronic respiratory disease with hospitalisation rate of 42 per 100 000 population,[21] and allergic rhinitis was the most commonly associated allergic disease.[22] Estimates of the impact of diseases on public health, generally referred to as burden of disease, may be valuable inputs for public health authorities, developing appropriate surveillance of fungal diseases and setting policy priorities. Disease burden should be considered as the underlying basis for prioritisation in Qatar.

The aim of this work is to compute and determine the burden of serious fungal infections in Qatar, in an attempt to estimates fungal disease frequency, which has not previously been attempted in this country.

Materials and methods

Qatar population

The primary study population consisted of residents of the state of Qatar in 2011. Data from this population were compared with data from previous population studies from Spain, Nigeria, USA and Korea.[23–26] The population and age distribution was obtained from 2011 WHO statistics.

Data source

Disease statistics were collected from the Microbiology laboratory database (MLD) based on details provided about clinical characteristics of the patients that were requested for mycology culture for in patients and out patients of Hamad Medical Corporation hospitals and clinics. Data on diseases were collected as the patients' main disease, which have the biggest burden for treatment among the patients' several diseases.

Categorisation of the targeted disease

Using the disease statistics from MLD, any patient who requested medical care under the disease code for a fungal infection as the primary diagnosis at least once during the 6-year period (from January 2009 to December 2014) were reported for this study. The annual prevalence of fungal infections was calculated by including patients with the disease, who had been treated multiple times were counted as one case per year in the data analysis. Laboratory diagnoses were collected from the only Mycology Laboratory in the country (January 2009 to December 2014).

Fungal infection can be categorised according to the International Classification of Diseases (ICD)-10, opportunistic mycoses (B37 Candidiasis, B44 Aspergillosis, B45 Cryptococcosis and B46 zygomycosis and B59 Pneumocystosis), which is a coding of diseases and signs, symptoms, abnormal findings, complaints, as classified by the World Health Organization (WHO). Based on these data, the prevalence's were calculated by dividing the number of patients with a fungal infection by the number of registered residents according to the Ministry of Development planning and Statistics, Qatar http://www.qsa.gov.qa/eng/populationstructure.htm for the years 2009–2014.

Calculation of fungal burden

In addition, all pertinent literature was obtained and assimilated. The population and age distribution formed the basis of the estimates for recurrent vulvovaginal candidiasis (rVVC) and expressed as 100 000 populations of females. The basis for the calculation of the rate of chronic pulmonary aspergillosis (CPA) was obtained from the WHO (2011 TB data)[27] and for 'fungal asthma' indirectly from childhood asthma rates.[28] Descriptive statistics were used to summarise the data, and expressed per 100 000 population. Allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitisation (SAFS) were calculated based on World Health Statistics 2013 (http://www.who.int/gho/publications/world_health_statistics/2013/en/). SAFS was estimated by assuming that 33% of the worst 10% of asthmatics are

sensitised to fungi (skin prick test or elevated fungal specific IgE).

Kaplan–Meier survival (product-limit method) estimates were used to generate the survival curve, and the median time to the event was used to assess and estimate the median survival time among the different *Candida* species.

Results

Population

Qatar is a country with an estimated population of 1 870 000 million people; 45.3% are men and 14% are children <15 years and only 2% of the population over 60 years. (http://www.qsa.gov.qa/eng/populationstructure.htm). The gross domestic product was $93 714 per person in 2013. HIV (70 cases) and TB (317 cases) rates are low. The total burden for non-*Aspergillus* and *Aspergillus* infections is 33 448 and 3574 respectively. Tables 1 and 2 shows the total burden of fungal infections, the number of infections classified according to the main risk factors as well as the rate for 100 000 inhabitants.

Non-*Aspergillus* infections

Candidaemia is the most prevalent non-*Aspergillus* invasive infection. Our records for the period 2009–2014 were reported from MLD showed 288 documented cases represented by a rate of 15.4 candidaemia cases per 100 000 inhabitants. The risk factors for infection are shown in Table 1 and include cancer burns, prior surgery and renal transplant. Kaplan–Meier estimates of survival at the 12 month follow-up after a positive blood culture are reported in Fig. 1. Candidaemia is associated with high crude mortality rate in Qatar. The overall crude 12-month mortality rate was 81.9% (125 out of 155 patients) for *Candida* species. The overall median survival rate among *Candida* species was 20 days (95% CI: 11.66–28.34 days).

We identified a total burden of 150 cases representing a rate of 8 per 100 000 inhabitants of *Candida* peritonitis/sterile body fluids. Most patients at risk are from ICU (n = 65), followed by patients with other medical risk factors (n = 37), patients with prior surgery (n = 32), renal transplant (n = 8) and patients with orthopaedic procedures (n = 6). The estimated burden of intra-ocular candidiasis is 2.05 per 100 000.

The prevalence of *Candida* vaginitis is the highest in Qatar; we estimate that 32 782 residential women

Table 1 Burden of non-*Aspergillus* fungal diseases in Qatar according to the main risk factor.

Infection	None (others)	Prior surgery	Other (medical)	Burn	Kidney/TX	Haematology/ oncology	Orthopaedic	ICU	HIV/immunocompromised	Total burden	Rate/100K
Cryptococcus meningitis	1	–	–	–	1	–	–	–	6	8	0.43
Pneumocystis pneumonia	–	–	–	–	–	–	–	–	15	15	0.8
Oral and oesophageal	70	–	–	–	1	40	3	8	–	122	6.52
Candidaemia	13	26	67	8	3	17	–	154	–	288	15.4
Recurrent *Candida* vaginitis	32 782	–	–	–	–	–	–	–	–	32 782	3506
Candida/peritonitis/sterile body fluids	2	32	37		8	–	6	65	–	150	8.02
Eye candidiasis	10	2	11	–	–	–	–	10	–	33	2.05
Mucormycosis	4	3	5	–	1	2	1	7	–	23	1.23
Fusarium	15			1	1	3			1	21	1.68
Fusarium keratitis	6									6	0.32
Total burden estimated	32 903	63	120	9	15	62	10	244	22	33 448	

Table 2 Burden of *Aspergillus* diseases in Qatar according to the main risk factor.

Infection	None (others)	Cancer/ immunocompromised	ICU	Respiratory	Orthopaedic	Renal impairment/ TX	Male/ female ratio	Total burden	Total (rate/100K)
Nail	255	0	0		1	0	2.2	256	14.77
Ear	364	2	36		0	1	1.43	403	23.26
Wound/ulcer/lesion	16	2	2		1	0	6	21	1.21
Rhinosinusitis	39	0	0		0	1	0.74	40	2.31
Tissue	17	1	3		0	0	4.25	21	1.21
Peritoneal/pleural/ other fluids	1	0	1		1	2	1.5	5	0.29
Skin	8	1	0		1	0	4	10	0.58
Eye	4	0	1		0	0	4	5	0.29
Invasive aspergillosis				11				11	0.60
Chronic pulmonary aspergillosis post TB				14				14	0.75
Chronic pulmonary aspergillosis – all				176				176	26.82
ABPA				1126				1126	60.2
SAFS				1486				1486	79.46
Total burden estimated	704	6	43	2813	4	4	3.015[1]	3574	

ABPA, allergic bronchopulmonary aspergillosis; SAFS, severe asthma with fungal sensitisation.

[1]Average figure for the male/female ratio.

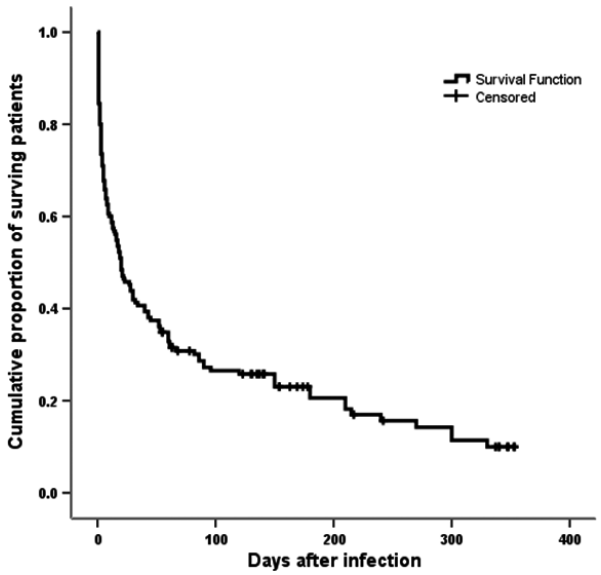

Fig. 1 Survival among patients with candidemia.

between the ages of 15 and 50 (although only 5866 are laboratory documented) get recurrent vaginal thrush, that is at least four times annually (Table 1). The total burden estimates of oral and oesophageal candidiasis was 122 cases with a rate of 6.52 per 100 000 inhabitants mostly in haematology/oncology patients (n = 40) and in immunocompetent individuals (n = 70). Other groups at risk are the ICU hospitalised patients in this study (n = 8), patients with orthopaedic procedures (n = 3) and renal transplant (n = 1).

Cryptococcus meningitis and *Pneumocystis* pneumonia were uncommon with a very low incidence. The annual incidence of cryptococcal meningitis cases according to the MLD in Qatar is 0.43 cases per 100 000; this is consistent with the low rate of HIV infection in this country. Most of the cases n = 6 (75%) occurred in HIV-positive patients, and one immunocompetent and one renal transplant patient. The rate of *Pneumocystis* pneumonia in HIV patients is 0.8/100 000, represented by only 15 cases, and is expected in Qatar due to low prevalence of the HIV/ AIDS disease.

The burden of infection per 100 000 inhabitants due to other pathogenic filamentous fungi, mucormycosis and *Fusarium* were estimated based on the MLD. We identified 23 cases of mucormycosis (1.23/ 100 000). Patients affected were those in the ICU (n = 7), cancer patients (n = 2), renal transplant recipients (n = 1), prior surgery (n = 3) and patients with other medical risk factors (n = 5). *Fusarium* is a highly pathogenic organism that infects immunocompetent (usually onychomycosis) patients and patients with neutropenia or post-transplant. We documented 27 cases, a rate of 1.68 per 100 000. Patients at risk of infections were cancer (n = 3), renal transplant

($n = 1$), HIV/immunocompromised ($n = 1$) and burn ($n = 1$). All other infections were nail and skin such as tinea pedis and intertrigo and in individuals with no apparent risk factor ($n = 15$). *Fusarium* cornea infections were reported in immunocompetent patients ($n = 6$). The total estimated burden for non-*Aspergillus* infections including *Candida* vaginitis was 33 448.

Aspergillus infections

Non-invasive *Aspergillus* infections are common in the population of Qatar. The majority are ear infections with an estimated rate of 23.3 per 100 000 inhabitants followed by onychomycosis with a rate of 14.8 per 100 000 (Table 2). Rhinosinusitis was reported in 40 patients representing a rate of 2.3 per 100 000; among these only one immunocompromised patient with a renal transplant was reported. Rare infections with wound, eyes and skin were reported (Table 2).

The risk factor for infection was not available for most respiratory Aspergillus infections. The estimated burdens (per 100 000) of invasive aspergillosis (IA) ($n = 11$) was 0.6, of chronic pulmonary aspergillosis post TB (CPA-TB) ($n = 14$) was 0.75 and all other CPA ($n = 176$) was 26.82. Fungal asthma, notably ABPA ($n = 1126$) was estimated to be more common at 60.2/100 000 and SAFS ($n = 1486$) at 79.46/100 000. The male-to-female ratio is always higher for different *Aspergillus* infections. Overall the number of males affected by aspergillosis was three-fold that of females. The estimated total burden of *Aspergillus* diseases is 3574 (Table 2).

Discussion

No comprehensive attempt to collate and estimate the incidence and prevalence of fungal disease in Qatar has been attempted. We have used real-life data come from either hospital-based retrospective studies[6] or case series of fungal infections derived from a laboratory database[29] to document the current status. We have supplemented these data with estimates, mostly derived from WHO statistics.

A retrospective study of candidaemia was performed in Qatar in the years 2004–2009 and found 187 documented cases[6] showed a rate of 12.9/100 000 inhabitants. However, during the later period reported here (2009–2014), cases of candidaemia rose to 288 with an estimated rate of 15.4. A real increase in the burden of candidaemia infections is therefore shown. This rate is more than that reported in some European countries. For example in Spain the rate was 8.1 per 100 000 inhabitants,[24] in Denmark it was 8.6[30] and in Norway and Finland there were three to five cases per 100 000 inhabitants.[31,32] In India, the incidence of candidaemia is 6.51 cases/1000 ICU admission, which probably equates to a rate of 21.1 per 100 000.[33] The United States also has very high rates, with up to 20 cases per 100 000 inhabitants.[34] In Qatar, 53.5% of all candidaemias ($n = 154$) occurred in ICU, a percentage higher than that reported in Spain (35.1%).[24] Non-ICU patients were also more likely to have neutropenia and to have received anti-cancer chemotherapy and immunosuppressive drugs. The severity of candidaemia is confirmed by the high crude mortality rate found in this survey (>60%), a figure similar to that reported recently in Brazil during clinical studies (60.8%),[35] and relatively higher than these reported in Saudi Arabia[36] and in a study series from Italy and Spain, where patients with candidaemia had a crude 30-day mortality rate of 39.9%.[37] The poor 1-year outcome of candidaemia (11% survival) we found in Qatar is a finding that needs replication elsewhere.

As many as 32 782 Qatari women between 15 and 50 years of age get recurrent *Candida* vulvovaginal thrush every year. Our rate is similar to the rate of vaginal candidiasis estimated in the Nigerian population (3800/100 000).[25]

As the HIV burden is fortunately low in Qatar, the rates of oral and oesophageal candidiasis was low. Most of the cases are non-HIV related and in other studies these rates have not been estimated. Remarkably in Korea, oesophageal candidiasis is documented in normal people,[38] and we identified a few such cases. It is challenging to estimate the total burden of oesophageal candidiasis given the range of underlying diseases associated with it. Likewise, low rates of *Cryptococcus* meningitis and *Pneumocystis* pneumonia reported in Qatar are attributable to low-HIV infection rates.

For mucormycosis, our study found an incidence rate of 1.23 cases per 100 000 inhabitants. However, in Spain and Nigeria, high population countries, the incidence was estimated at only 0.04 and 0.2 per 100 000 inhabitants, which is probably underestimated in both countries. The high prevalence of diabetes in Qatar (16.3/100 000) (www.idf.org/membership/mena/qatar) as well as other risk factors, such as ICU patients, might be responsible for the high rate of mucormycosis.

Fusarium is an emerging pathogenic fungus, which is reported to cause skin infections in Qatar,[39] was found with relatively high burden represented by 1.23 cases per 100 000. This organism was also

responsible for invasive infections in immunocompromised patients. Cutaneous infections were reported particularly in patients with no immune deficiency. Most patients were from high-risk areas of the world, in particular, India and South East Asia. Fusariosis represents the second most common cause of filamentous fungi infections after aspergillosis, with 97 cases reported in the literature between January 2000 and January 2010, updated with additional 26 cases in November 2013.[40]

Documented cases of non-invasive infections of *Aspergillus* were obtained from our MLD. Infections of the ear, nail, skin and wounds are common in the population of Qatar. In Iran, a nearby Middle East country, 29.2% of the non-dermatophyte onychomycosis was attributed to *Aspergillus* infections.[41] Aspergillosis of the ear may be complicated by malignant underlying disease,[42] but this is rare. *Aspergillus* rhinosinusitis is represented by a relatively high rate in Qatar (2.31/100 000) due to some climatic factors including humidity and atopic young patients that develop allergic type of *Aspergillus* rhinosinusitis.[17,18] Our laboratory data do not capture risk factors for IA, but in any case the rate is very low.

Asthma has a high prevalence of 5% to 10%.[43] There has been an increase in prevalence, rate of asthma, and mortality among adult and children. This increasing trend in morbidity and mortality has been reported in a number of countries, including Saudi Arabia, USA and Europe.[44–46] The disease may appear at any age, but is most common in childhood. Previous study showed a high prevalence of asthma (19.8%) in Qatari school children,[47] whereas in hospitalised adults the rate was 42 per 100 000 inhabitant.[21] Fungal complications of asthma such as SAFS affect 1486 people, ABPA 1126 people and CPA 176 people. ABPA and SAFS were estimated to be relatively high rates in Qatar compared with other fungal diseases, 60.2 and 79.46 per 100 000 inhabitants respectively. These figures are lower than that reported for other countries.[24] Because Qatar population is extremely mixed and mobile with workers from high-risk areas, asthma and respiratory infections might be attributed to several factors, including sub-tropical desert hot summer climate, climate socioeconomic factors, psychosocial dysfunction of patient or family, patient with impaired immune systems and underestimation of asthma severity or respiratory infection by the patient or the physician.

CPA-TB is uncommon, as TB is not a common problem in Qatar. CPA and pulmonary tuberculosis may exist,[48] but more commonly, CPA follows TB, partly as a result of residual cavitation post TB.[27] Additional work to document the cases of CPA not attributable to prior TB needs to be done to establish the burden of CPA in Qatar.

Very few imported and unusual fungal infections have been documented in Qatar. Notably no cases of histoplasmosis, coccidioidomycosis or *Talaromyces marneffei* infections have been documented over the last 5 years.

In conclusion, the epidemiology and burden of fungal infections in Qatar is still not completely documented. Surveillance of fungal infections is important in Qatar and we have partial data for the country. Based on the information provided above, guidelines are needed to focus on fungal infections in Qatar. In addition, a fungal registry system needs development for monitoring infections and surveillance.

Acknowledgments

Supported by Grant NPRP 5-298-3-086 from the Qatar National Research Fund (a member of Qatar Foundation) to Saad J. Taj-Aldeen.

Conflict of interest

ST-A and PC declare no conflict of interest. DWD 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 Allergy and Infectious Diseases, National Institute of Health Research, NorthWest Lung Centre Charity, Medical Research Council, Astellas and the Fungal Infection Trust. He acts as a consultant to T2 Biosystems, GSK, Sigma Tau, Oxon Epidemiology and Pulmicort. 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. He is also President of the Global Action Fund for Fungal Infections.

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