Estimated burden of fungal disease in Uganda

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Abstract

Background

In Sub-Saharan Africa, the HIV epidemic has highlighted cryptococcal and candida infections as important opportunistic fungal infections. However, the burden of other fungal diseases is not well described. Estimating the burden of these infections in Uganda is important first step to identify gaps in diagnosis, care and treatment for fungal infections.

Methods

All epidemiological papers of fungal diseases in Uganda were reviewed. For infections where there is no local data, global data was used. Population statistics were obtained from World Bank. HIV statistics from the Uganda AIDSindicators survey (UAS) 2009, pregnancy rates from the UMRP, and TB from WHO database (as 2010).

Results

Estimates have largely relied on National statistics for the population and other conditions. Without more comminucable diseases including respiratory conditions and malignancies. Therefore, in Uganda, we have been able to revise our local data to a population of 32,000,000. These data were used to estimate the burden of fungal disease in Uganda.

Non HIV related estimates were revised based on local publications. While non HIV related fungal infections have been more described, the burden of non HIV related fungal infections is not well described. We have used previously described calculations by the Uganda National Surveillance Report 20113, stated the following: There are an estimated 1,100,000 infected with HIV in Uganda.

Invasive aspergillosis

There are no good epidemiological estimates on leukaemias or COPD in Uganda. Invasive aspergillosis affects 148,000. We have estimated 10% of all fungi on ART are estimated to be 24,584.4.

Conclusion

Whilst we estimate the burden of fungal disease in Uganda specifically, the estimates for the burden of fungal disease globally become increasingly important. However, all the global infectious disease global and regional data. Nevertheless, there is a substantial burden of fungal infection in Africa (estimated 1100x3000) 2300x3000 per year. Given this large burden fungal disease is relatively understudied. We need to urgently address gaps in knowledge, diagnosis, and management of fungal disease in Sub-Saharan Africa.

References

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Background

• Estimates of fungal infection caseloads are required to plan and implement healthcare policies.
• Healthcare in Israel: Universal healthcare system.
• Five tertiary-level medical centers provide specialized medical care.
• Epidemiological trends: A growing medical tourism industry.
• Immigration from Africa.
• Increase in the population of patients cared at tertiary hospitals.
• Increasing rates of newly diagnosed TB and HIV/AIDS.

Objectives

• Estimate national fungal infection caseloads in Israel from epidemiological datasets.

Methods

• We searched national data available from the Israeli ministry of health, WHO and OECD reports, as well as surveillance studies published by us and other authors for relevant disease terms.

Methods (ctd.)

• Locally collected incidence data were available for candidaemia, HIV/AIDS, solid organ and stem cell transplantation, TB, asthma, COPD and cystic fibrosis.
• When no specific data were available, fungal disease rates were estimated from incidence rates in susceptible populations.
• Generally, disease estimates were conservative as they assumed the lowest incidence rates reported in the literature and focused only on well-defined risk populations.

Results

• Israel’s population (2011):
  • 7.8 Million
  • median age 29 yrs
  • 34% <18 yrs, 10% ≥65 yrs
• Population prevalence of chronic respiratory disease:
  • COPD, 312,000, asthma, 375,000, cystic fibrosis, 468.
  • Pulmonary tuberculosis: 345/yr.

<table>
<thead>
<tr>
<th>Table 1: Fungal infection burden estimates for Israel</th>
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<tbody>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Oesophageal candidiasis [AI]</td>
</tr>
<tr>
<td>Candidaemia [AI]</td>
</tr>
<tr>
<td>Recurrent vaginal candidiasis (&gt;4/year) [AI]</td>
</tr>
<tr>
<td>ABPA [P]</td>
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<tr>
<td>SAFS [P]</td>
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<tr>
<td>Chronic pulmonary aspergillosis [P]</td>
</tr>
<tr>
<td>Invasive aspergillosis [AI]</td>
</tr>
<tr>
<td>Mucormycosis [AI]</td>
</tr>
<tr>
<td>Pneumocystis pneumonia [AI]</td>
</tr>
</tbody>
</table>

AI, annual incidence; P, prevalence

Total burden: 151,833

Conclusions

• Vaginal candidiasis and ABPA dominate the burden from the fungal infection in Israel, whereas candidaemia and invasive aspergillosis are the most frequent causes of fatal infection.
• These data should help guide empirical treatment choices and preventive actions at the national level.

References

The burden of serious fungal infections in the Netherlands

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Introduction:
Although the healthcare system in the Netherlands is advanced, the number of invasive (mucosal) fungal infections is unknown. By using numbers of patients at risk for fungal infections we have estimated the potential burden of serious fungal infections in the Netherlands.

Methods:
Population data and published papers from the Netherlands were extracted from the following websites:
www.cbs.nl (Centraalbureau voor de Statistiek)
www.nationaalkompas.nl
www.cijfersoverkanker.nl
www.ncfs.nl (Cystic Fibrosis Foundation)
www.hiv-monitoring.nl
www.transplantatiestichting.nl (National Transplant Registry)
www.peritonitis.nl
www.nivel.nl

Results:
Amongst a population of 16,766M, 17.3% are children (0-14 years) and 21% of the population are >60 years old. Recurrent vaginal thrush (>4 times annually) affects 5% of women under 50, an estimated total of 219,588. Of the 1073 cases of pulmonary TB in 2011, 96% HIV negative, 45 new cases of chronic pulmonary aspergillosis (CPA) cases are estimated, a 5-year period prevalence of 142 CPA cases, 25% of all cases (assuming 15% annual mortality). Asthma prevalence in adults is 7.2% (997,378 cases) although 2003 figures suggest 519,800. Assuming that 2.5% of the lower number have ABPA, 13,085 patients with ABPA are likely and 17,153 have severe asthma with fungal sensitisation (SAFS). Of the 16,555 estimated HIV positive patients, only 812 presented with AIDS in 2011 and none developed Pneumocystis pneumonia or cryptococcal meningitis. Estimating the annual incidence of Pneumocystis pneumonia or oesophageal candidosis in other patient groups was not possible.

The rate of candidaemia was estimated at 5/100,000 population consistent with 838 cases. Candida peritonitis is estimated at 50% of the ICU candidaemia rate, itself estimated to be 70% of all candidaemia. Among haematological/transplant and COPD patients, invasive aspergillosis is estimated at 336 and 240 respectively.

<table>
<thead>
<tr>
<th>Infection</th>
<th>Number of infections per underlying disorder per year</th>
<th>Total burden</th>
<th>Rate /100K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophageal candidosis</td>
<td>- 1200</td>
<td>1200</td>
<td>7.2</td>
</tr>
<tr>
<td>Candidaemia</td>
<td>- - 251</td>
<td>838</td>
<td>2.6</td>
</tr>
<tr>
<td>Candida peritonitis</td>
<td>- - 235</td>
<td>235</td>
<td>0.9</td>
</tr>
<tr>
<td>Recurrent vaginal candidosis (&gt;4x/year)</td>
<td>219,588</td>
<td>219,588</td>
<td>2612</td>
</tr>
<tr>
<td>ABPA</td>
<td>- - 13,085</td>
<td>13,085</td>
<td>78</td>
</tr>
<tr>
<td>SAFS</td>
<td>- - 17,153</td>
<td>17,153</td>
<td>102</td>
</tr>
<tr>
<td>Invasive aspergillosis</td>
<td>- - 336</td>
<td>336</td>
<td>577</td>
</tr>
<tr>
<td>Mucormycosis</td>
<td>- - 34</td>
<td>34</td>
<td>0.2</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>- - 0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
<td>- - ?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

Total burden estimated 219,588 1200 30,808 2171 622 254,010

Conclusion:
Serious fungal infections in the Netherlands occur in immunocompromised patients and those with underlying pulmonary diseases. Validation of estimates of numbers can be achieved with future surveillance studies.
Background & Objective

With a vulnerable population greater than 110 million and a stark absence of surveillance machinery in India, determining valid, comparable, evidence-based fungal burden estimates is of paramount importance. Such comprehensive baseline data is useful for effective prioritization of our public health resources. We have developed a probabilistic model for estimating mucormycosis burden, wherein our aim was to estimate its overall prevalence, syndromic burden, circulating species, underlying risk factors and mortality indices.

Methods

Search strategy: Indian literature spread across five decades (1960-2012) was mined from international (MEDLINE, BIREME, ProMed, Cochrane, ERIC), national (IndMed) and WHO regional databases using multiple combinations of relevant keywords like “mucormycosis”, “zygomycosis”, “India”, etc. Current metrics on total Indian population and burden of HIV/AIDS, TB, COPD, cancer, diabetes, transplant, critical care, trauma and surgeries were extracted from national and international census data. All searches were closed on 5 April 2013.

Selection criteria: The retrieved literature was systematically reviewed and sorted as per precise criteria pertaining their case definitions, study design, setting, time period, sampling protocol, population denominators, geographical location, diagnostic test efficacy, statistical tests and outcome reliability and validity. The quality of study selection, data extraction was controlled by independent reviewers, among the authors. The entire search, selection and extraction process was guided by the PRISMA and MOOSE guidelines.

Modelling: A deterministic model was designed keeping our objectives in mind. Given the availability of accurate Indian population estimates of diabetes, we chose diabetes as the most reliable denominator and multiplier for building the model. The meta-analyzed mucormycosis effect sizes for each risk factor were incorporated into the model to derive burden projections for each at-risk population. The model was further extended using syndrome, species and mortality specific effect sizes to derive burden estimates for corresponding mucormycosis subgroups. All estimates in the model were adjusted for sensitivity and specificity of mucormycosis diagnostic tests.

Uncertainty analysis: Uncertainty intervals were set via bootstrapping and random factors like time period variations, sampling variations and binning bias were included. Probabilistic modelling using Monte Carlo algorithms can efficiently and often completely negate such uncertainties, which meta-analytic and stochastic models may fail to achieve. We identified input variables in our deterministic model which were potentially prone to uncertainty. Raw data distribution fitting was used to determine and assess distribution patterns influencing each input variable. Next, the output variables were identified and incorporated into the probabilistic model. Monte Carlo analysis was used to simulate the model for 1000 iterations and generate probabilistic burden estimates for mucormycosis. All calculations were performed using Palisade@Risk v5.5 and @RISK v5.1.

Results

We found 908 studies on Indian mucormycosis patients. 59% of which were excluded as duplicates. The remaining 365 abstracts were reviewed in line with our inclusion criteria and 49 potentially useful studies were retrieved. These studies were finally screened for meta-analysis and modelling.

Mucormycosis prevalence and mortality: Our computational model reveals a mucormycosis prevalence of 0.14 cases per 1000 population in India. The cumulative burden range between 208,177 and 137,507 cases with a mean of 171,504 (SD: 12,365.6; 95% CI: 195,777 -147,688) (Fig 1). The mean attributable mortality was 54,580 (38.2%) deaths per year (95% CI: 73,412 - 57,998). (Fig 2A) Subgroup analysis showed highest mortality rate (mean 20,860 per year; 31.8%) among rhinocerebral cases and least mortality risk in cutaneous infections (total 0.023 per 1000 population; 0.015% (95% CI: 0.018 – 0.010) (Fig 1B).

Risk factor - syndrome analysis: Calculations reveal that diabetes is the most common risk factor for nearly all forms of mucormycosis, but does not predispose to isolated nasal disease. It contributes to the largest number of rhinocerebral cases (mean 16,865 cases; 95% CI: 73,687 - 83,633). The second largest at-risk population are apparently healthy individuals most prone to developing renal mucormycosis (mean 11,596 cases; 95% CI: 13,272 - 10,409) besides cutaneous (mean 5,462 cases; 95% CI: 6,297 - 3,608) and rhinocerebral mucormycosis (mean 7,330 cases; 95% CI: 8,191 - 6,833) disease. Disseminated mucormycosis has the highest burden among diabetes (mean 7,184 cases; 95% CI: 7,902 - 6,346) with substantial hospitalization among cases, transplant, trauma and surgical cases as well. Gastrointestinal disease similarly was noted to be common among trauma, surgery and diabetes patients. (Fig 6).

Discussion

Mucormycosis is a fast emerging fungal infection in India. Our study brings forth vital data on its burden not only in terms of total prevalence and mortality, but also its clinical-microbiological ramifications. Our colossal diabetic population of 50 million (90.70% being uncontrolled), rapid progress in modern medical care, pathological hospitalizations, interventional interventions and increasing reliance on antibiotic and antifungal prophylaxis have fuelled the rise of these fungi. Our annual mucormycosis stands at 201.13 million cases. The overall mortality rate of 38.2% when examined closely is marked by 93.6% and 64.4% mortality rates in disseminated and gastrointestinal disease, respectively.

Our burden estimates also highlight certain peculiarities possibly unique to India. a) Diabetes bear nearly half (51.2%) of our total projected burden, with millions more among uncontrolled population. b) Unlike the developed world, we have a substantial burden of isolated nasal mucormycosis (mean 16,865 cases) and only a negligible number of fulminant (0.1% in 2011 cases). While we also have the highest number of rhinocerebral cases (17,330 cases), extremely less common syndromes have shown limited prevalence and severity, which is in stark contrast to western reports. c) Diabetes is the commonest risk factor in our data, and it also points to the substantial burden of mucormycosis. A recent study has noted that diabetes is the commonest risk factor in mucormycosis in India. We also note that diabetes prevalence is directly related to the tropical climates of the Indian subcontinent.

Our burden estimates and geo-contextual settings call for greater attention among diabetics and apparently healthy individuals presenting with nasal complaints. It also alerts us to strengthen our diagnostic services to enable early detection of even uncommon syndromes. Our data also aims to enhance the clinical and public health fraternity to the substantial burden of mucormycosis. Better awareness in tandem with aggressive investigation and management can bring down the mortality drastically among rhinocerebral, gastrointestinal and disseminated mucormycosis.

Conclusion

Our novel computer-based computational estimations offer valuable fungal burden data so far unavailable with all national and international health authorities. This comprehensive data is contextually relevant to our population, country's epidemiology, fungal distribution and underlying risk factors. Our computations assume study state demographic and pathogen dynamics, a shortcoming we have partially circumvented using Monte-Carlo probabilities.

Select References

Our estimates indicate that over 11.8% of the Nigerian population is estimated to suffer from a serious fungal infection each year. If tinea capitis and recurrent vaginal thrush are excluded, over 80,000 are estimated to be affected, with substantial morbidity. Epidemiological studies are urgently required to validate or modify these estimates.

Invasive fungal infections have emerged worldwide as an increasingly frequent cause of opportunistic infections [3]. The incidence of nosocomial fungal infections has continued to rise over the past two decades in parallel with advances in medical and surgical procedures resulting in considerable morbidity and high mortality rate [4,5]. Bone marrow and solid organ managed in our environment. Total burden estimated 17,941,657 times empirical therapy is used.

There is a dearth of data from Nigeria on the burden of fungal infection rates from Nigeria. We used specific populations at risk and fungal infection frequencies in the population to estimate national incidence or prevalence where no relevant studies were available. HIV population statistics of 2008, the 2011 WHO HIV infection and AIDS treatment rates. National Agency for the Control of AIDS, Ministry of Health, Nigeria. There were few epidemiological data on serious fungal infections in Nigeria.

We therefore estimated the burden of serious fungal infections in Nigeria based on the populations at risk.

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Discussion

- Invasive fungal infections (IFIs) are frequently life-threatening infections with high morbidity and mortality rates. The groups of patients at risk are critically ill; haematological children [10], and about 1,500,000 women with recurrent vaginal candidiasis [11].
- Our findings revealed a number of epidemiological reports on superficial and mucocutaneous fungal infections with an estimated total burden of 15,581,400 cases of tinea capitis in children [10], and about 1,500,000 women with recurrent vaginal candidiasis [11].
- We estimated 74,594 cases of Pneumocystis pneumonia from data from other African studies which were predominantly in the HIV/AIDS pediatric age group.
- The prevalence of blindness in Nigeria is 0.78% with corneal opacities accounting for 12% (15); however there are no data on fungal keratitis in Nigeria a country with a huge population of rural dwellers and farmers.

- There have been no proactive searches for these life-threatening infections probably due to the fact that patients pay for every stage of their management in the hospital so most times empirical therapy is used.
- Conventional diagnostic tests such as direct microscopy, histopathology and culture are routinely used, but not galactomannan, β-D-glucan, or DNA-detection tests and this may have impacted on the ability to diagnose invasive fungal infections.
- Epidemiological data on the burden of fungal infections in our environment will be of public health impact and influence the management protocol of the groups of patients at risk.
Burden of serious fungal infections in Spain

Abstract

All published epidemiology papers reporting fungal infection rates from Spain were identified. Where no data existed, we used specific prevalence figures. The estimated annual incidence rate of 0.04 cases/100,000 inhabitants that suggests 20 cases every year. The number of people with asthma and allergic bronchopulmonary aspergillosis (ABPA) is estimated at 2.5% based on 5 previous studies (9). The rate of SAFS was estimated as the worst 10% of the total asthma population. It was assumed that tuberculosis (TB) was the underlying diagnosis of CPA in 25% of cases. The number of people with CD4 counts (33,750 cases), and oesophageal candidiasis in 20%. Therefore, 67,500 cases of oral candidiasis and 11,250 of oesophageal candidiasis are expected annually. Respiratory infections: In table 2 the number of IA in allogeneic and solid organ transplanted patients is shown. Table 3 shows the incidence, prevalence, and the number of IA cases. In 2010, at least 247 cases were identified. Therefore, in transplanted and haematological patients, 342 new cases of CPA occurred and that the 5-year period prevalence is 1,079 cases (assuming 15% annual mortality). As total CPA cases as estimated that 342 new cases of CPA occurred and that the 5-year period prevalence is 1,079 cases (assuming 15% annual mortality). Therefore, 67,500 cases of oral candidiasis and 11,250 of oesophageal candidiasis are expected annually.

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Results

Country profile: Spain has a country population of 47 millions of people. Of the 150,000 estimated HIV positive patients, 21% women (http://www.msc.es/novedades/docs/InformeVIH-sida Junio 2011.pdf). The University of Manchester in association with the LIFE program at www.LIFE-worldwide.org

Conclusions

Epidemiology of fungal infections in Spain is uncertain with an exception, candidemia where two population-based studies have been performed in the last decade. Apart from cutaneous fungal infections and Pneumocystis pneumonia, most fungal infections are not transmitted from person to person. Most are acquired from the environment or in the case of Candida from endogenous gut faecal flora. Some are therefore unavoidable. No vaccines are available.

As none fungal infection is considered modifiable the current records rely on epidemiologic studies performed for different institutions but in many cases, the rates have been calculated based on the frequencies of fungal infections in patients at risk. In addition, there is no information about YLDs that fungal infection causes a crucial parameter in the prevention and monitoring of health. Around 7.6 million people suffer fungal infections each year in Spain. Most of them are skin or mucosal infections causing no deaths. However, the number of YLDs of skin fungal infections is 1.4 million per year. For dermatophytosis, incidence can be estimated in 10 to 20 years per year.

Fungal infections with a high mortality as IA or candidemia are not numerous in Spain (631 annual cases) but they affect a population with severe underlying diseases that worsen the outcome. The incidence of IA is uncertain with an estimated 100 cases per year from endogenous (gut) flora. Most are therefore unavoidable. No vaccines are available.

LIFE (www.LIFE-worldwide.org) has launched an initiative in many countries in order to calculate the burden of fungal diseases following a similar approach. We will obtain some preliminary data with the aim of developing a model that facilitates the performance of better epidemiologic studies that allocate the right resources for the group of infections that are not even considered as "neglected diseases." We have estimated that worldwide attributable fungal infections (1,350,000 cases) are as high as those produced by tuberculosis (1,400,000) and malaria (1,240,000) (20), two priority diseases in the global health agenda.

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