Estimating fungal infection burden in India using computational models: Mucormycosis burden as a case study

Arunaloke Chakrabarti,[1] Prashant Sood,[2] David Denning[3]
Postgraduate Institute of Medical Education and Research,[1] Chandigarh, India; All India Institute of Medical Sciences,[2] New Delhi, India; University Hospital of South Manchester,[3] Manchester, United Kingdom

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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 are of paramount importance. Such comprehensive baseline data is useful for effective prioritization of our public health resources. We have developed contextual computational models for elucidating 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, transplants, 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 and data extraction was controlled by inter-rater reliability, among the authors. The entire search, selection and extraction process was guided by the PRISMA and MOOSE guidelines.

Meta-analysis: Short-listed studies were assessed for heterogeneity using Cochran's Q and I-square statistics. Accordingly, each effect size was computed by meta-analysis using either the fixed-effects model for homogeneous data or the DerSimonian Laird random-effects model for heterogeneous data.

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 interposes through unknown and known factors like time period variations, sampling variations and binning bias. Probabilistic modelling using Monte Carlo algorithms can offset and often completely negate such uncertainties, which meta-analysis 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 ascribe distribution patterns influencing each input variable. Next, the output variables were identified and incorporated into the probabilistic model. Monte Carlo analysis using Latin hypercube sampling 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 SPSS v21.

Results

We found 908 studies on Indian mucormycosis patients. 539 of these were excluded as duplicates. The remaining 369 abstracts were reviewed in line with our inclusion criteria and 49 potentially useful studies were retrieved. Nine studies were finally chosen for meta-analysis and modelling.[1-5]

Mucormycosis prevalence and mortality: Our computational model reveals a mucormycosis prevalence of 0.14 cases per 1000 population in India. The cumulative burden ranges between 208,177 and 137,807 cases with a mean of 171,504 (SD: 12,365.6; 95% CI: 195,777 - 147,688) (Fig 1). The mean attributable mortality was 65,500 (38.2%) deaths per year (95% CI: 73,402 - 57,989) (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 (mean 2,922 per year; 4.5%) (Fig 2B).

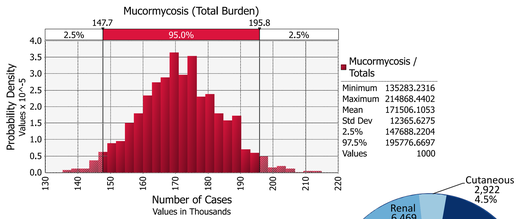


Figure 1: Probabilistic model depicting the total burden and dispersion of mucormycosis in India

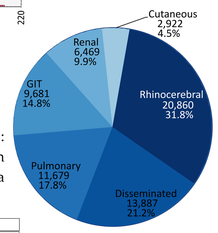
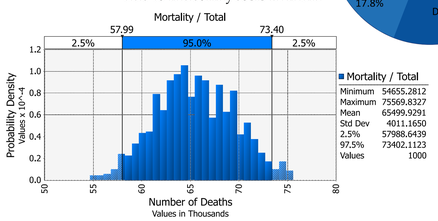


Figure 2A-B: Total mortality distribution due to mucormycosis in India



Distribution in at-risk populations: Estimates specific for underlying risk factors reveal mean burden of 77,874 (95% CI: 84,020 - 71,905) cases among diabetics, 18,625 (95% CI: 20,603 - 17,443) cases among cancer and transplant patients, 8,566 (95% CI: 9,527 - 8,026) cases among trauma, major surgery and intensive care patients, 794 (95% CI: 1,452 - 770) cases among tuberculosis and COPD patients, 286 (95% CI: 286 - 173) cases among HIV/AIDS patients and 44,949 (95% CI: 58,787 - 31,224) cases among individuals with no apparent underlying disease. Diabetes (51.3%) stands out as the most important risk factor (Fig 3).

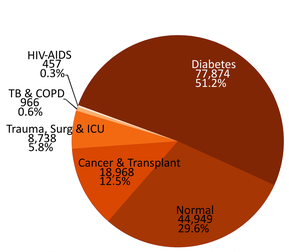


Figure 3: Mucormycosis burden in different at-risk populations of India

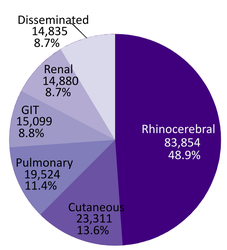


Figure 4: Clinical syndromes of mucormycosis in India

Syndromic burden: The largest mean burden was noted for rhinocerebral disease with 83,854 cases (48.9%; 95 CI: 93,409 - 74,347), and least mean burden was among disseminated disease with 14,835 cases (8.6%; 95% CI: 16,525 - 13,167). Burden estimates for other syndromes revealed 23,311 cutaneous cases (95% CI: 26,062 - 20,764); 19,524 pulmonary cases (95% CI: 21,865 - 17,367); 15,099 gastrointestinal infections (95% CI: 16,862 - 13,437); and 14,880 isolated renal cases (95% CI: 16,619 - 13,116) (Fig 4).

Species distribution: *Rhizopus oryzae* is the commonest isolate with 1,01,661 cases annually (59.3%; 95% CI: 1,13,431 - 90,597) followed by *Apophysomyces elegans* with mean 44,439 cases (25.9%; 95% CI: 49,487 - 39,289) per year. Other less common species are estimated to contribute a mean 25,403 cases per year comprising the remaining 14.8% cases of mucormycosis in India (Fig 5).

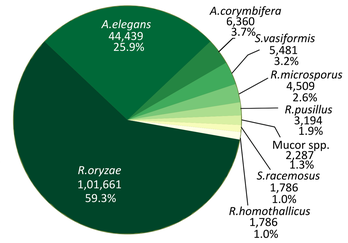


Figure 5: Contribution of different species to mucormycosis burden in India

Risk-factor vs. syndrome analysis: Calculations reveal that diabetes is the most common risk factor responsible for nearly all forms of mucormycosis, but does not predispose to isolaated renal disease. It contributes to the largest number of rhinocerebral cases (mean 66,865 cases; 95% CI: 73,687 - 58,633). The second largest at-risk population are apparently healthy individuals, most prone to developing renal mucormycosis (mean 11,929 cases; 95% CI: 13,272 - 10,639) besides cutaneous (mean 5,641 cases; 95% CI: 6,297 - 5,028) and rhinocerebral (mean 7,333 cases; 95% CI: 8,191 - 6,553) disease. Disseminated mucormycosis has the highest burden among diabetics (mean 7,104 cases; 95% CI: 7,920 - 6,346) with substantial footprint among cancer, transplant, trauma and surgical cases as well. Gastrointestinal disease similarly was noted to be common among trauma, surgery and diabetes patients. (Fig 6).

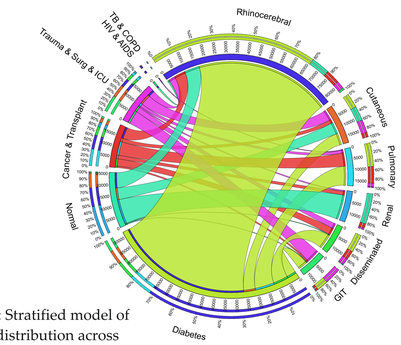


Figure 6: Stratified model of burden distribution across at-risk populations and mucormycosis syndromes in India

Species vs. syndrome analysis: *R. oryzae* is the most common agent of mucormycosis in India, contributing to all forms of the disease, with highest burden among rhinocerebral patients (mean 85,405 cases; 95% CI: 95,018 - 75,100). The second most common is *A. elegans* which inflicts all forms disease except pulmonary mucormycosis. Its largest burden is noted among cutaneous mucormycosis (mean 21,822 cases; 95% CI: 24,282 - 19,457). *R. oryzae* and *A. elegans* together contribute to the entire burden of renal and disseminated mucormycosis in India. *A. corymbifera*, the third most common pathogen, tends to cause mainly rhinocerebral disease (mean 6,360 cases; 95% CI: 7,084 - 5,674), while all other less common pathogens have their footprint largely on cutaneous and rhinocerebral forms of mucormycosis (Fig 7).

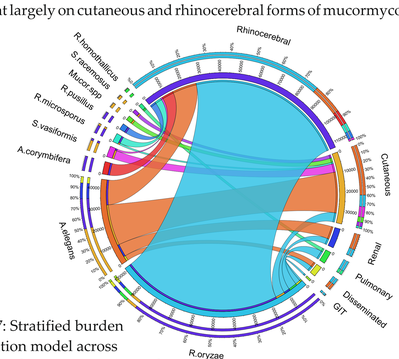


Figure 7: Stratified burden distribution model across species and mucormycosis syndromes

Discussion

Mucormycosis is a fast emerging fungal infection in India. Our study brings forth vital data to gauge its burden not only in terms of total prevalence and mortality, but also its clinico-microbiological ramifications. Our colossal diabetic population of 50 million (50-70% being uncontrolled), rapid progress in modern medical care, prolonged hospitalizations, intravenous interventions and increasing reliance on antibiotic and antifungal prophylaxis have fuelled the rise of these fungi. Our annual mucormycosis stands at 0.20 - 0.13 million cases. The overall mortality rate of 38.2% when examined closely is marked by 93.6% and 64.1% mortality rates in disseminated and gastrointestinal disease, respectively.

Our burden estimates also highlight certain peculiarities possibly unique to India. a) Diabetics bear nearly half (51.2%) of our total projected burden, with nearly 57.3% of these among our rural population. b) Unlike the developed world, we have a substantial burden of isolated renal mucormycosis (mean 14,880 cases per year). Interestingly the large majority of these cases (80.1%; mean 11,292 cases) are apparently immunocompetent with no underlying risk factors. c) *R. oryzae* and *A. elegans* together inflict the entire burden of renal and disseminated mucormycosis in our country. d) *A. elegans* is also the second most common pathogen among our cases, and has been observed to cause all forms of mucormycosis other than pulmonary disease. We believe this is peculiar to the tropical climes of the Indian subcontinent.

Our burden estimates and geo-contextual settings call for greater attention among diabetics and apparently healthy individuals presenting with renal complaints. It also alerts us to strengthen our diagnostic services to enable early detection of even uncommon zygomycetes. Our data also aims to sensitize 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 rate especially among rhinocerebral, gastrointestinal and disseminated mucormycosis.

Conclusion

Our evidence-based computational estimates 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, fungi distribution and underlying risk factors. Our computations assume steady state demographic and pathogen dynamics, a shortcoming we have partially circumvented using Monte Carlo probabilities.

Select References

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