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.

Methods

Search strategy: Indian literature search across five decades (1960-2012) was mined from international (MEDLINE, BIREM, ProMed, Cochrane, EDOC) national (PubMed) and WHO regional databases using multiple combinations of relevant keywords such as “mucormycosis”, “zygomycosis”, “India”, etc. Current metrics on total Indian population and burden of HIV/AIDS, TB, COPD, cancer, diabetes, even, critical care trauma and surgeries were extracted from national and international resources data. All searches were closed on 3 April 2015.

Selection criteria: The retrieved literature was systematically reviewed and noted as per precise criteria pertaining to 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 control and data extraction was conducted by independent raters. 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 syndromes, species and mortality specific effect sizes to derive burden estimates for corresponding mucormycosis subgroups. All sensitivity and data were adjusted for sensitivity and specificity of mucormycosis diagnostic tests.

Uncertainty analysis: Uncertainty intervals through unknowns and known factors like time period variations, sampling variations and biasing factors. Prevalent modeling using Monte Carlo algorithms can offset and often completely negate such uncertainties, which meta-analysis and stochastic modeling may not achieve. We identified input variables into our deterministic model which were potentially prone to uncertainty. Randomized 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 using Latin hypercube sampling was used to estimate the model for 100 iterations and generate probability burden estimates for mucormycosis. All calculations were performed using RStudio version 1.1.456 and R(3.5.1).

Results

We found 908 studies on Indian mucormycosis patients. 339 of these were excluded as duplicates. The remaining 569 abstracts were reviewed in line with our inclusion criteria and 88 potentially useful studies were retrieved. Nine studies were finally chosen for meta-analysis and modeling.

Mucormycosis prevalence and mortality: Our computational model reveals a mucormycosis prevalence of 0.14 cases per 1000 population in India. The cumulative burden rates range between 289,177 and 377,857 cases with a mean of 313,304 (95% CI: 323,685 - 303,977) per year. The mean attributable mortality was 65,300 (58.2%) deaths per year (95% CI: 75,402 - 57,989) (Fig 1). Subgroup analysis showed highest mortality rate (80,860 per year; 31.8%) among rhinocerebral cases and least mortality risk in cutaneous/subcutaneous cases (15.52 per 1000; 8.8%) (Fig 2B).

Species distribution: Rhizopus species is the consequent isolate with 125,461 cases annually (93.79%, 95% CI: 1.13-1.45); 80,979 followed by Apophysomyces elegans with (cases 64,439 cases (25.5%, 95% CI: 49,487 - 52,169) per year. Other less common species are estimated to contribute a mean 25,858 cases per year comprising the remaining 14.8% cases of mucormycosis in India (Fig 5).

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 preclude to isolated nasal disease. It contributes to the largest number of rhinocerebral cases (mean 66,685 cases; 95% CI: 73,667 - 59,630). The second largest at-risk population are apparently healthy individuals, most prone to developing renal mucormycosis (mean 13,329 cases; 95% CI: 13,272 - 13,683) besides cutaneous (mean 12,486 cases; 95% CI: 12,209 - 12,762) is also rhinocerebral (mean 7,207 cases; 95% CI: 8,192 - 6,234). Disseminated mucormycosis has the highest burden among diabetics (mean 7,038 cases; 95% CI: 7,305 - 6,448) with substantial hospital 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).

Discussion

Mucormycosis is a fast emerging fungal infection in India. Our study brings forth vital data to gauge the burden not only in terms of prevalence and mortality, but also its clinico-microbiological ramifications. Our national diabetes population of 30 million (90-70% being uncontrolled), rapid progress in cancer and organ transplant hospitals, immunosuppressive interventions and increasing reliance on antibiotic and antifungal prophylaxis have fuelled the rise of these fungi. Our annual mucormycosis stands at 0.20-0.115 million cases. The overall mortality rate of 32.4% when examined closely is by 93.6% and 64.4% mortality rates is 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 burdens, with nearly 97.8% of these among our rural population. b) Unlike the developed world, we have a substantial burden of isolated renal mucormycosis (mean 15,486 cases per year). Interestingly, the large majority of these cases (98.1% mean 12,925 cases) are apparently immunocompromised with no underlying risk factors. c) Of organ and A. elegans together reflect the entire burden of renal and disseminated mucormycosis in our country. d) A. elegans takes the second most common pathway 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 climates of the Indian subcontinent.

Our burden estimates and geo-contextual settings call for greater attention among diabetics and apparently healthy individuals presenting with renal complains. It also allows us to strengthen our diagnostic services to enable early detection of even uncommon mucormycosis. Our data also aims to sensitize the clinical and public health hierarchy to the substantial burden of mucormycosis. Better awareness in doctors 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 as unfeasible with all national and international health authorities. This comprehensive data is coherently relevant to our population, country’s epidemiology, fungal distribution and underlying risk factors. Our computations assume steady state demographic and pathogens dynamics, a shortcoming we have partially circumvented using Monte Carlo probabilities.

Select References