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MAJOR ARTICLE

Burden of Serious Fungal Infections in India

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Background. Fungal disease is frequent in India, but its incidence and prevalence are unclear. This review aims at defining the frequency or burden of various fungal infections in India.

Methods. A systematic review of the literature on the PubMed, Embase, and Web of Science (WOS) databases was conducted using appropriate search strings. Deterministic modeling determined annual incidence and prevalence estimates for multiple life- and sight-threatening infections with significant morbidity.

Results. Literature searches yielded >2900 papers; 434 papers with incidence/prevalence/proportion data were analyzed. An estimated 57 251 328 of the 1 393 400 000 people in India (4.1%) suffer from a serious fungal disease. The prevalence (in millions) of recurrent vulvovaginal candidiasis is 24.3, allergic bronchopulmonary aspergillosis is 2.0, tinea capitis in school-age children is 25, severe asthma with fungal sensitization is 1.36, chronic pulmonary aspergillosis is 1.74, and chronic fungal rhinosinusitis is 1.52. The annual incidence rates of *Pneumocystis* pneumonia (58 400), invasive aspergillosis (250 900), mucormycosis (195 000), esophageal candidiasis in HIV (266 600), candidemia (188 000), fungal keratitis (1 017 100), and cryptococcal meningitis (11 500) were also determined. Histoplasmosis, talaromycosis, mycetoma, and chromoblastomycosis were less frequent.

Conclusions. India's fungal burden is high and underappreciated in clinical practice.

Keywords. *Aspergillus*; *Candida*; *Cryptococcus*; histoplasmosis; mycetoma; *Pneumocystis*; sporotrichosis; tinea capitis.

Globally, fungal diseases are known to impact millions of lives [1]. However, the epidemiology of fungal infections varies in different geographical regions, being dependent on multiple factors including at-risk individuals, socioeconomic attributes, and fungal endemicity related to geo-ecological characteristics, all leading to substantial impacts on health [2]. India is the second most populous country in the world and the seventh largest country by land area [3]. This tropical country has unique and diverse geographical characteristics, with mountains, plains, plateaus, and numerous rivers, in addition to being surrounded on three sides by vast stretches of ocean [4].

Many fungal infections are endemic in India, and several pathogens found globally are frequently isolated there [5]. The presence of fungal disease has been implicated from ancient times in the Indian subcontinent; the Atharva Veda, an ancient Hindu scripture written between 1500 and 500 BCE, mentions mycetoma ("pada valmikam," or "anthill foot)" in the Indian population [6]. The first case of histoplasmosis was reported in Calcutta in 1954 [7], followed by gradual recognition of the impact of other fungal diseases in this population. Several host characteristics, such as a very high incidence of pulmonary tuberculosis (PTB) [8], malignancies, chronic pulmonary obstructive disease (COPD) [9], and others, also contribute to a high predilection for fungal diseases in the Indian population. Many outbreaks of different fungal infections have been periodically reported from different parts of India, including *Candida auris* [10] and, more recently, COVID-19-associated mucormycosis [11, 12]. The challenges posed by the evolving health care system of this developing country result in significant morbidity and mortality caused by the gamut of fungal diseases, which, however, has not been categorically quantified.

There are published estimates of fungal disease burden in India for certain conditions including chronic pulmonary aspergillosis (CPA), allergic bronchopulmonary aspergillosis (ABPA) [13], and other global burden estimates that include India, namely cryptococcal meningitis in HIV [14], fungal keratitis [15], and recurrent vulvovaginal candidiasis [16]. However, no concerted attempt has been made to holistically estimate the fungal burden in this country with >1.3 billion people. In this study, we have systematically studied the

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incidence and prevalence of serious fungal infections in India, together summarized as burden.

METHODS

A thorough review of the existing literature was done for screening studies on fungal epidemiology in India. For diseases where no relevant studies could be identified, burden of infection was calculated based on other studies pertaining to specific populations at risk from world literature. An overview of the methodology adopted is described in Figure 1.

Population Data of At-Risk Population

Estimates of India's total population segmented by adult, pediatric, female, aged 14–49 years, and other parameters were obtained from United Nations Population Division (2021) [17]. The data on HIV/AIDS in India were obtained from the National AIDS Control Organization (NACO) database [18]. The World Health Organization tuberculosis report was referred to for obtaining data on the burden of tuberculosis patients [8]. Malignancy incidence was retrieved from various sources including the Global Burden of Disease Study [19], while data about transplant recipients were derived from the National Organ and Tissue Transplant Organization (NOTTO) [20]. Population estimates of COPD and asthma prevalence were taken from the 2018 Global Burden of Disease estimates [9]. Details are given in Table 1.

Incidence and Prevalence Data From Selection Studies

A systematic review of the literature on the PubMed, Embase, and Web of Science (WOS) databases was conducted using appropriate search strings (Appendices 2–5). Studies published in English pertaining to the incidence/prevalence data of different fungal organisms and conditions from inception until April 31, 2021, were included. Where India-specific prevalence or incidence data were not found, estimates were extrapolated from published global data. Details are given in Table 2.

Aspergillosis Burden Estimations

The burdens of invasive aspergillosis (IA), chronic pulmonary aspergillosis (CPA) [26], ABPA, and severe asthma with fungal sensitization (SAFS) were estimated. IA burden was separately estimated in hematological malignancy, hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT), lung cancer, COPD, and AIDS patients. Total cases of acute myeloid leukemia (AML) were estimated to be 40% of the total burden of leukemia and myeloma. The annual incidence of acute myeloid leukemia is 25 224 cases [39]. The rate of IA in AML patients receiving induction chemotherapy was 13% [27], and an equal number of cases of IA was assumed in all other cases of leukemia and myeloma [28]. The incidence of IA in lung cancer was assumed to be 2.6% [30]. The IA rates were assumed be 10% for HSCT recipients, while for SOT the rates were 2%, 4%, 6%, and 20% for kidney, liver, heart, and lung transplants, respectively [29]. For IA in AIDS patients, a 4% incidence of those who died was assumed [32]. The estimated total number of COPD cases in India (in 2021) was 58 million, with a population prevalence of 4.2% [9] and an annual incidence of IA of 1.3%–3.9% (Supplementary Data 1, ref. 29) [21, 30].

The estimated total number of asthma cases in adults in India in 2021 was ~40 million (2.9% prevalence in adults in 2016) [9]. The burden of ABPA was assessed using ~5% prevalence in asthma patients [13]. The proportion of severe asthma was assumed to be 10%, and the fungal sensitization rate was taken to be 33% [29]. We were not able to estimate ABPA or severe asthma with fungal sensitization prevalence in children, although they occur. As a small number of patients with cystic fibrosis reach adolescence in India, the number contributing to ABPA was not thought to be significant enough to warrant consideration (Supplementary Data 6, ref. 2). Chronic fungal rhinosinusitis prevalence was based on a population study in India [34].

The WHO Global Tuberculosis report [8] was used for the estimated pulmonary TB burden in India. The following assumptions were made in the calculation of CPA burden [26]: (a) coinfection of CPA with confirmed TB is 7% in HIV-positive and 3% in HIV-negative patients; (b) proportions of CPA among patients thought to have TB but unconfirmed in patients with and without HIV are 10% and 19%, respectively; (c) the proportion of CPA in patients at the end of TB therapy is 10%; (d) 22% of PTB patients have 1 or more residual cavities at the end of therapy (Supplementary Data 6, ref. 3); (e) 6.5% and 0.2% of patients with and without cavities annually develop CPA 2–5 years after completion of antituberculous therapy, 20% of patients with CPA succumb in the first year, and 7.5% succumb annually thereafter. We assumed that 90% of CPA cases were directly linked to current or prior TB (Supplementary Data 6, ref. 27). The full details of this model are published separately [26].

Mucormycosis

The annual incidence of mucormycosis was estimated from previously published Indian data at 14/100 000 [38]. Furthermore, it was assumed that 55% of cases are related to poor diabetic control and 45% of cases are related to other factors, notably hematological malignancy, transplantation, and other immunocompromised states. The burden of COVID-associated mucormycosis (CAM) was estimated from published literature.

Candidiasis Burden Estimations

The annual incidence of candidemia, *Candida* peritonitis (intraabdominal candidiasis), and esophageal candidiasis in HIV-infected people and the prevalence of recurrent vulvovaginal candidiasis (RVVC) were estimated. For calculating the prevalence of invasive candidiasis, incidence in intensive care

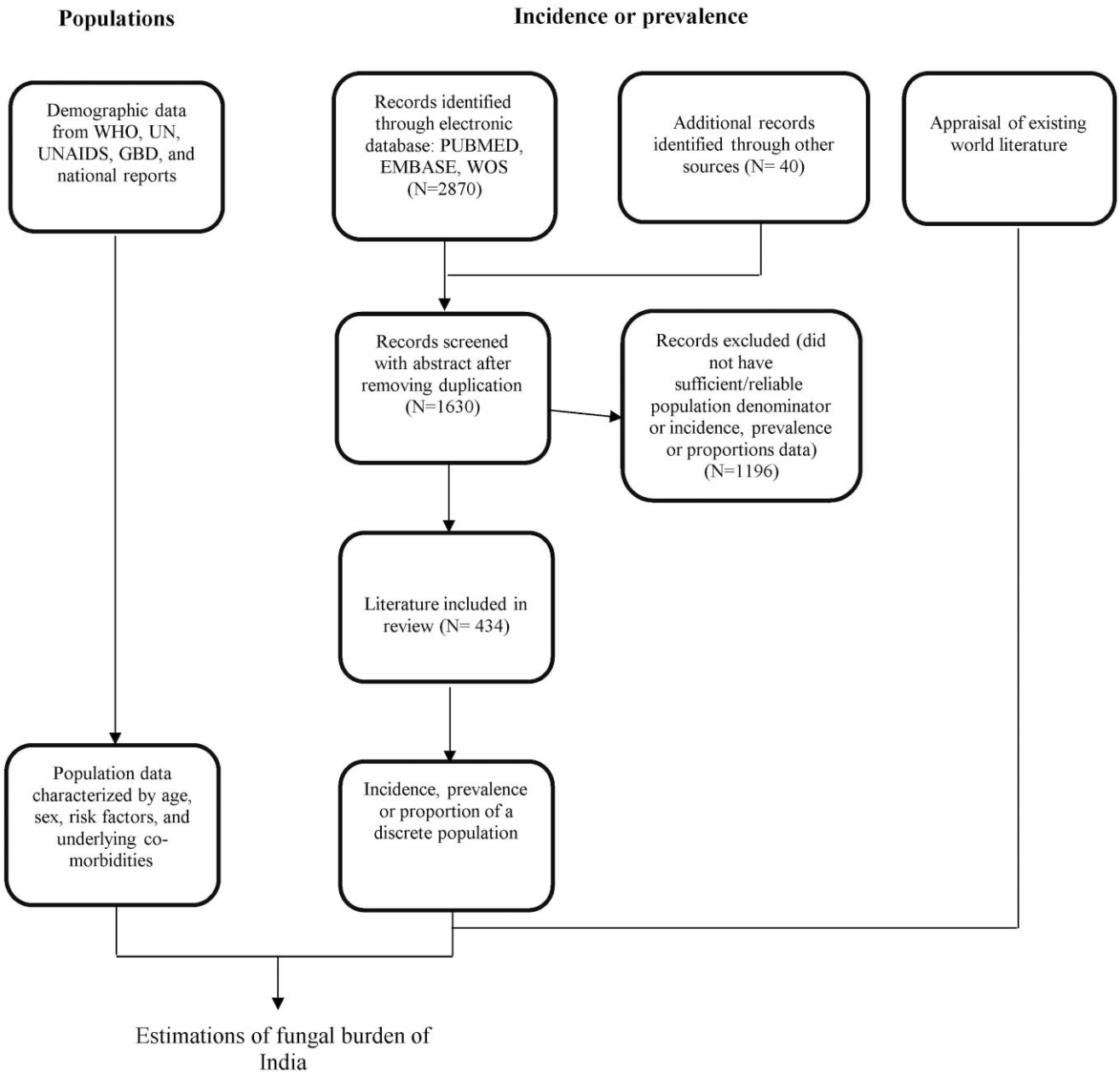

Figure 1. Flowchart showing the methodology adopted for estimating the fungal incidence and prevalence in the Indian population. Abbreviations: CPA, chronic pulmonary aspergillosis; PTB, pulmonary tuberculosis; TB, tuberculosis.

units (ICUs) was first assessed. The annual incidence of candidemia outside of the ICU in Asia was ~4 times that occurring in the ICU [35]. There are no data on incidence of candidemia in neutropenic patients in the currently available literature from India. Also, 1 episode of intraabdominal candidiasis usually occurs per 2 episodes of candidemia in the ICU [40]. The rate of *Candida* peritonitis in chronic ambulatory peritoneal dialysis (CAPD) was assumed using available estimates. For RVVC, the rate was assumed from a recent world-wide estimate to be 6% of all adult women, not including postmenopausal women on hormone replacement therapy [16]. Esophageal candidiasis was assumed to occur in 5% and 20% of patients with HIV on and not on ART, respectively; estimation in non-HIV patients was not attempted [29].

HIV-Related Infection

Burden Estimations

The annual incidence rates of *Pneumocystis* pneumonia (PCP), cryptococcal meningitis (CM), talaromycosis, and histoplasmosis were estimated. Numbers of HIV patients living with CD4 <200 cells/mm^3 were estimated from NACO data using a 7-year decline in CD4 count plus a 5% proportion with

Table 1. Population Characteristics in India, by Age, Gender, High-risk Factors, and Underlying Diseases

Population Characteristic	No. in Thousands	Reference
Total population	1 393 400 000	https://www.unfpa.org/data/world-population-dashboard
Population of children 0–14 y	359 497 200 (25.8%)	https://www.unfpa.org/data/world-population/IN
School-going children 5–14 y	250 533 320 (17.98%)	https://en.wikipedia.org/wiki/Demographics_of_India
Total adults (59.29%)	826 146 860	https://en.wikipedia.org/wiki/Demographics_of_India
Sex ratio (M/F) F %	1102/1000 (47.57%)	Undata | Record View | Sex Ratio at Birth (Male Births per Female Births) https://en.wikipedia.org/wiki/Demographics_of_India
Female population, 15–49 y	352 896 218 (53.24% of total females)	UNdata | Record View | Sex Ratio at Birth (Male Births per Female Births) https://en.wikipedia.org/wiki/Demographics_of_India
Adult women	406 176 100 (29.15% of total females)	https://en.wikipedia.org/wiki/Demographics_of_India
People with HIV	2 349 000	http://naco.gov.in/sites/default/files/Sankalak%20Status%20of%
Proportion of HIV patients on ART	1 479 870 (63%)	http://naco.gov.in/sites/default/files/Sankalak%20Status%20of%
Adults with HIV and CD4 <200 cells/μL	963 090 (41%)	Late HIV Diagnosis (With Initial CD4 Cell Count <200 cells/mm^3) (%) countryfactsheetsindia2020change.pdf
AIDS-related deaths	58 960	UNAIDS_INDIA HIV ESTIMATES-2.indd (naco.gov.in)
Annual cases of TB (includes HIV + TB)	2 590 000 (1780–3550)	https://worldhealthorg.shinyapps.io/tb_
Annual cases of TB in HIV + TB	53 000	https://worldhealthorg.shinyapps.io/tb_
Mortality, deaths (excludes HIV + TB)	493 000	https://worldhealthorg.shinyapps.io/tb_
Mortality, deaths (HIV + TB only)	11 000	https://worldhealthorg.shinyapps.io/tb_
Annual cases of pulmonary TB (without HIV) who survive at the end of 1 y	1 451 240	https://worldhealthorg.shinyapps.io/tb_
Annual cases of pulmonary TB (with HIV) who survive at the end of 1 y	29 820	https://worldhealthorg.shinyapps.io/tb_
Adult population with asthma (2.9% of adult population)	40 408 600	[9]
Total COPD (4.2% of population)	58 522 800	[9]
Total COPD admitted to hospital each year (10.5% of COPD)	6 144 894	[21]
Lung cancer (2016 data prevalent cases)	72 150	India Cancer Incidence Globocan International Agency for Research on Cancer 2020 https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf
Liver transplants per year (2019)	728	https://notto.gov.in/organreport.htm
Renal transplants per year (2019)	2234	https://notto.gov.in/organreport.htm
Lung transplants per year (2019)	50–100	[22]
Heart transplants per year (2019)	125	https://notto.gov.in/organreport.htm
Allogeneic stem cell transplants per year	19 000	[23]
Acute myelogenous leukemia (2017)	25 224	356-india-fact-sheets.pdf https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf
No. of patients on peritoneal dialysis	8500	[24]
Intensive care unit beds	94 961	COVID-19 in India: State-wise Estimates of Current Hospital Beds, Intensive Care Unit (ICU) Beds and Ventilators" by Geetanjali Kapoor, Aditi Sriram, Jyoti Joshi, Arindam Nandi, and Ramanan Laxminarayan
Intensive care admissions surviving >24 h	6 d	[25]

Abbreviations: ART, antiretroviral therapy; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; TB, tuberculosis.

resistance to antiretroviral therapy. The at-risk population was therefore conservatively estimated at 198 000 people. We assumed the frequency of PCP in patients with AIDS to be 13% [36]. The rate of CrAg positivity in people with HIV (PWH) was assumed by taking a mean of 5.9% in those with CD4 <100 cells/mm^3. The corresponding rate for patients with CD4 between 100 and 200 cells/mm^3 was assumed to be 65% of the rate in those with CD4 <100 cells/mm^3, that is, 3.8%, and it was assumed that without screening all eventually develop meningitis. On average, the frequency of CM was assumed to be 4.9% of the total patients at risk. CM in HIV-infected people was assumed to comprise 84% of total CM patients [31].

A systematic review was done to identify all the talaromycosis cases reported from India. The burden of talaromycosis was estimated to be 1.43% of newly presenting advanced HIV disease in Northeast India, based on a large systematic review [37]. We systematically searched for all studies from India reporting >5 cases of histoplasmosis, but could not compute an overall burden, given substantial regional variation in histoplasmosis.

Table 2. Assumptions and Calculations for the Estimations of Fungal Disease Burden, India

Fungal Diseases	Assumptions	Calculations/Total Patients	Reference
RVVC	Assumed to occur in 6% of all adult women	RVVC = adult women × 6%	[16]
IA	a. AML is estimated to account for 40% of annual incidence of all leukemias and myelomas, and IA is assumed to occur in 13% of patients with AML	IA = a + b + c + d + e	[27, 28]
	b. IA rates were assumed be 10% for HSCT recipients, while for SOT the rates were 2%, 4%, 6%, and 20% for kidney, liver, heart, and lung transplants, respectively	…	[29]
	c. IA occurs in 2.6% of lung cancer patients	…	[30]
	d. IA occurs in 3.9% of hospitalized COPD patients	…	[31]
	e. IA accounts for 4% of total HIV deaths	…	[32]
CPA	See text in Methods: 90% of CPA cases are linked to TB	…	[33]
ABPA	ABPA is prevalent in 5% of adult asthmatics	ABPA = asthmatics × 5%	[9]
SAFS	Assumes 33% of most severe10% of adult asthmatics	SAFS = population with asthma × 33% × 10%	[29]
Allergic fungal rhinosinusitis	Assumes that 0.11% of the population are affected	Total population × 0.11%	[34]
Candidemia	Candidemia episodes in critically ill patients = (ICU beds × 365/median length of ICU stay)×rate of candidemia in ICU/1000 admissions	Candidemia = candidemia episodes in ICU/0.25	[35]
Candida peritonitis	Rate of *Candida* peritonitis is 50% of cases of candidemia in ICU	*Candida* peritonitis = candidemia in ICU × 50%	[29]
Candida peritonitis CAPD	Out of all patients on CAPD, the overall infection rate was 0.27 episodes/patient/y, and 3.7% of all such infections were *Candida* peritonitis	*Candida* peritonitis = peritoneal dialysis × 0.27 × 3.7%	…
Esophageal candidiasis	Assumed to occur at the rate of 5% in HIV patients on ART and 20% of those not on ART	Esophageal candidiasis = 5% of HIV on ART + 20% of HIV not on ART	[29]
CM	CM occurred in 5% of HIV patients with CD4 <200 cells/cm while the burden in non-HIV patients was assumed to be 16% of total CM patients	CM = (5% of HIV with CD4 < 200)/0.84	[31]
PCP	PCP occurred in 13% of HIV patients with CD4 <200, and PCP in non-HIV assumed to be 56% of total PCP	PCP = (13% of HIV with CD4 < 200)/0.44	[36]
Talaromycosis	Incidence thought to be 1.43% of newly presenting advanced HIV disease	1.43% of HIV with CD4 < 200	[37]
Histoplasmosis	Not estimated due to absence of country-specific data	…	…
Mucormycosis	Assumed to occur at the rate of 14/10 000	…	[38]
Fungal keratitis	Assumed to occur in 73/100 000 of total population	Fungal keratitis = 0.007% of total population	[14]
Tinea capitis infections	Estimated to occur in 10% of school-going children	Tinea capitis = 10% of school-going population	(Suppl. 6, ref 6).

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; AML, acute myeloid leukemia; CAPD, chronic ambulatory peritoneal dialysis; CM, cryptococcal meningitis; COPD, chronic pulmonary obstructive disease; CPA, chronic pulmonary aspergillosis; HSCT, hematopoietic stem cell transplant; IA, invasive aspergillosis; ICU, intensive care unit; IPA, invasive pulmonary aspergillosis; PCP, *Pneumocystis* pneumonia; RVVC, recurrent vulvovaginal candidiasis; SAFS, severe asthma with fungal sensitization.

Neglected Tropical and Other Skin Diseases Burden Estimation

Recent publications described the published cases of mycetoma [41], chromoblastomycosis [42], and sporotrichosis (Supplementary Data 6, ref. 4). These were used for describing the occurrence of these conditions in India, but could not be used to accurately assess prevalence. A prevalence estimate of tinea capitis was also made from available Indian literature. A recent systematic global analysis of the incidence and outcome of fungal keratitis was recently published [15] and was used to estimate this sight-threatening condition.

Epidemiology Maps

For talaromycosis and histoplasmosis, epidemiology maps were constructed to depict the number of reported cases in India (Supplementary Data 4). For drawing the maps, a thorough review of the existing Indian literature was conducted on the MEDLINE, Embase, and Web of Sciences databases. Search strategy details and an individual summary of each identified publication can be found in Appendices 1–5.

RESULTS

According to the data published by the United Nations, the population of India in 2020 was 1.39 billion, with females comprising 47.57%. The population of children (0–14 years) was estimated to be 25.8%. The proportion of school-going children (5–14 years) was assumed to be ~69.7% of the 0–14-year-old population. The number of people living with HIV infection (PWH) was estimated to be 2.35 million, with ~37% naive to antiretroviral therapy (ART) and ~41% newly diagnosed patients having advanced HIV disease or AIDS. The estimates of the population characteristics and high-risk populations are detailed in Table 1. A summary of the results is given in Table 3.

Aspergillosis Burden

COPD affects 58 million adults with GOLD stage 2–4 annually (4.2%), and an estimated 6 million are hospitalized annually. The annual incidence of IA in COPD patients was conservatively

estimated to be between 79 100 cases (assuming an attack rate of 1.3%) and 239 000 cases (assuming an attack rate of 3.9%) There were an estimated 72 510 lung cancer cases in India in 2020, of which 2.6% were assumed to have developed invasive IA, a total of 1885. An additional 7040 IA cases are likely among those with leukemia, lymphoma, and post-transplantation. Assuming none of the probable cases of IA complicating HIV infection would be diagnosed, an additional 2360 cases were assumed among the 59 000 deaths from AIDS in 2020. Therefore, the annual IA incidence was estimated at 250 900 cases or 17.9/100 000 population.

Both mistaken for (usually smear/GeneXpert negative) and as a dual infection with tuberculosis, an annual incidence of 212 502 CPA patients were expected, or 15.3/100 000, of whom an 42 766 died in that first year after presentation (Figure 3). An additional 149 733 patients developed CPA toward the end of their 6 months of therapy or in the few months thereafter. In years 2–5 after antituberculous therapy, an additional 21 211 cases arose annually. Assuming a 20% first year mortality rate and 7.5% thereafter, and given the unchanging number of pulmonary TB cases in prior years, the 5-year period prevalence of CPA related to tuberculosis was estimated at 1 564 570 (112 per 100 000), with an additional 99 984 deaths. The burden of CPA associated with PTB was thought to represent 90% of the total burden of CPA, pegging the total CPA prevalence in India at ~1 738 913 (125/100 000).

Among the estimated 40 million adult asthmatics, the number of people with SAFS is estimated at 1.36 million. The calculated ABPA prevalence ranges from as low as 1 million (2.5%) to 2 million (5%) and as high as 2.8 million (7%). We have not estimated the prevalence of either SAFS or ABPA in children, although both conditions occur (Supplementary Data 6, refs. 20–25).

A population-based study in the Punjab and Haryana provinces (which had a slightly higher referral rate than other areas) found 0.11% of the entire population to have chronic fungal rhinosinusitis (FRS) [34]. Across India, this translated into 1.52 million affected. Of the 29% with chronic rhinosinusitis who underwent detailed evaluation, 27.2% were diagnosed with FRS, of whom 56.1% had allergic FRS, 17.8% chronic granulomatous FRS, 15.0% eosinophilic FRS, 9.5% a fungal ball, and 1.3% chronic invasive FRS.

Mucormycosis Incidence

The relatively high prevalence of diabetes in India, which is often poorly controlled, contributes to the world's highest incidence of mucormycosis at 14/100 000 [38]. Therefore, we estimated about 195 000 cases annually. This was made evident by the recent COVID-19 pandemic, with an additional 40 000 cases reported through July 2021 (Supplementary Data 6, ref. 5). The primary pathogens (pre-COVID-19) were *Rhizopus arrhizus* (>50%), *Rhizopus microsporus*, *Apophysomyces variabilis*, and *Rhizopus homothallicus*.

Candidiasis Burden

In 2020, there were ~94 961 ICU beds in India [43], and the rate of candidemia according to a large multicenter study done between April 2011 and September 2012 was 6.51/1000 ICU admissions [44]. The median length of stay was assumed to be 6 days on the basis of a prevalence study in 124 ICUs in 2010–2011 [25]. Thus, there were estimated 37 607 candidemia episodes in the ICU and a total of 188 035 cases per year (13.6/100 000). Blood cultures are ~40% sensitive for the diagnosis of invasive candidiasis, so the annual incidence of invasive candidiasis is ~470 000 or 34/100 000 population.

Candida tropicalis is the commonest species (~42%) found in blood culture, with *C. albicans* accounting for ~21% of cases. *Candida auris*, an emerging pathogen, was estimated to comprise ~5.3% of cases based on a large multicenter study conducted between April 2011 and September 2012 [10].

There is a large number of end-stage renal disease patients in India on renal replacement therapy, of whom ~8500 were on CAPD at any one time [45]. The rate of peritonitis in these patients was assumed to be 0.39 episodes/patient year [46], and it was assumed that *Candida* caused ~2.2% of infections [47]. Thus, the total number of *Candida* peritonitis patients annually was ~85 patients. In the ICU, the incidence of postsurgical intra-abdominal candidiasis was estimated at 18 775 cases per year.

The prevalence of RVVC was estimated to be ~24 370 566 cases annually (1749/100 000 women). The annual incidence of esophageal candidiasis was estimated at 73 994 cases for PWH on ART and 192 618 for PWH not on ART, a cumulative incidence of 266 612 cases annually. We have not been able to estimate incidence in non-HIV populations.

HIV-Related Infection Burden

We estimated total PCP patients in India to be ~58 378, with 25 686 in HIV and 32 691 in non-HIV patients, respectively. The annual incidence was calculated as 4.19/100 000 population. Around 11 526 cases of cryptococcal meningitis (CM) were estimated to occur annually, with 9682 in HIV patients and 1844 in non-HIV patients, respectively. Our systematic review identified a total of 132 talaromycosis patients from India. The total number of talaromycosis cases in HIV patients was estimated to be 2825 assuming that talaromycosis occurred in 1.43% of newly presenting cases of advanced HIV disease. We identified a total of 316 cases (in studies reporting >5 cases) of histoplasmosis from a review of the literature in India, including 43 cases in HIV, 111 cases with adrenal involvement, and four cases of pulmonary involvement. However, an estimate of total histoplasmosis cases in India could not be made due to unavailability of relevant data and the localized occurrence of the disease. Epidemiological maps of histoplasmosis are shown in Figure 2*A* and Figure *B*. The maps have value in showing areas of higher incidence of histoplasmosis, although calculation of the total incidence is not possible with the current data.

Table 3. Summary of Fungal Infection Burden in India According to Major Risk Factors

Infection	No. Infections per Underlying Disorder per Year					Total No. Cases	Rate/100 000 Population
	None/ Others	HIV/ AIDS	Respiratory	Cancer/ Immune-compromised	ICU/ Surgery		
RVVC	24 370 566	…	…	…	…	24 370 566	1749
IA	…	2358	1885[c]	7040[c]	239 651[a]	250 935	18
CPA	…	…	1 738 913	…	…	1 738 913	125
ABPA	…	…	1 197 913	…	…	1 197 913	86.0
SAFS	…	…	1 363 142	…	…	1 363 142	97.8
Fungal rhinosunusitis	1 518 005	…	…	…	…	1 518 005	109
Mucormycosis	107 292	…	…	87 784	…	195 076	14.0
Candidemia	…	…	…	150 427	37 607	188 035	13.5
Candida peritonitis ICU + surgery	…	…	…	…	18 803	18 803	1.35
Candida peritonitis CAPD	85	…	…	…	…	85	0.004
Esophageal candidiasis	…	192 618	…	…	…	266 612	19.1
Cryptococcal meningitis	1844	9682	…	…	…	11 526	0.83
Pneumocystis pneumonia	…	25 686	…	32 691	…	58 378	4.19
Talaromycosis	…	2825	…	…	…	2825	0.2
Fungal keratitis	1 017 182	…	…	…	…	1 017 182	73.0
Tinea capitis	25 053 332	…	…	…	…	25 053 332	1798
Total serious fungal infection	…	…	…	…	…	**57 251 328**	**4109**

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; AML, acute myeloid leukemia; CAPD, chronic ambulatory peritoneal dialysis; COPD, chronic pulmonary obstructive disease; CPA, chronic pulmonary aspergillosis; IA, invasive aspergillosis; ICU, intensive care unit; IPA, invasive pulmonary aspergillosis; RVVC, recurrent vulvovaginal candidiasis; SAFS, severe asthma with fungal sensitization.

[a]Includes IPA in hospitalized COPD patients.

[b]Includes lung malignancy.

[c]Includes AML, non-AML hematological conditions, transplant recipients (lung, liver, kidney, heart, stem cell). Totals in bold.

Burden of Neglected Tropical and Other Skin Diseases

A total of 448 cases of sporotrichosis were reported from India. The predominant pathogen is *Sporothrix globosa* (Supplementary Data 6, ref. 4). Sporotrichosis cases are endemic to the sub-Himalyan regions, including the Himachal Pradesh, Uttarakhand, West Bengal, Sikkim, Assam, Manipur provinces, although cases have been reported throughout the country [48]. It was not possible to provide a national annual incidence of sporotrichosis.

There were 1116 cases of mycetoma reported from India [41] and 169 cases of chromoblastomycosis [42]. It is not possible to estimate annual incidence or prevalence from these reported cases.

There have been multiple studies of tinea capitis in the Indian population, but actual population prevalence studies are not present. The only population-based survey from India showed the prevalence of tinea capitis among 10% of all urban primary school children in Kolkata (Supplementary Data 6, ref. 6). The prevalence of tinea capitis among all superficial mycosis patients presenting to hospital specialist services varies between 2% to 14% (Supplementary Data 6, refs. 7–8), with most studies reporting close to 5% prevalence among all dermatophytosis cases (Supplementary Data 6, refs. 9–13). Among all tinea capitis cases, children represent 90% of cases, and 70% of cases occurred in lower income groups (Supplementary Data 6, refs. 6, 14–16). We estimate 25 053 332 (1798/100 000) cases, assuming the Kolkata data apply across the country.

Annually, fungal keratitis was estimated to afflict 73 per 100 000 people [15], or 1 017 182 persons. This estimate is consistent with a 1993 study in Madurai that found the annual incidence of corneal ulceration to be 113/100 000 in the survey population of 3.5 million in Madurai (Supplementary Data 6, ref. 17). The majority of cases of corneal ulceration are caused by fungi in India (40%–80%) (Supplementary Data 6, ref. 18). Many of these cases will result in unilateral and sometimes bilateral blindness. In rural India, a recent survey found that 0.55% of the population had either unilateral or bilateral corneal opacity and blindness in the affected eye [49].

DISCUSSION

We estimated a total of 57 250 826 patients to be affected by serious fungal diseases in India. Around 4.1% of the Indian population is probably affected, which is similar to reports from other countries like China, Brazil, Korea, Senegal, and Germany (Supplementary Data 6, ref. 19). This total burden of serious fungal infections is >10 times the annual incidence of tuberculosis in India, indicating an enormous population of patients affected by fungal diseases.

Overall, our estimates are probably conservative. Candidemia represents only 40% of invasive candidiasis, as blood cultures are not very sensitive, and even less so in patients already on antifungal therapy. A possible reason for the high proportion of candidemia in non-ICU patients may be a shortage of ICU

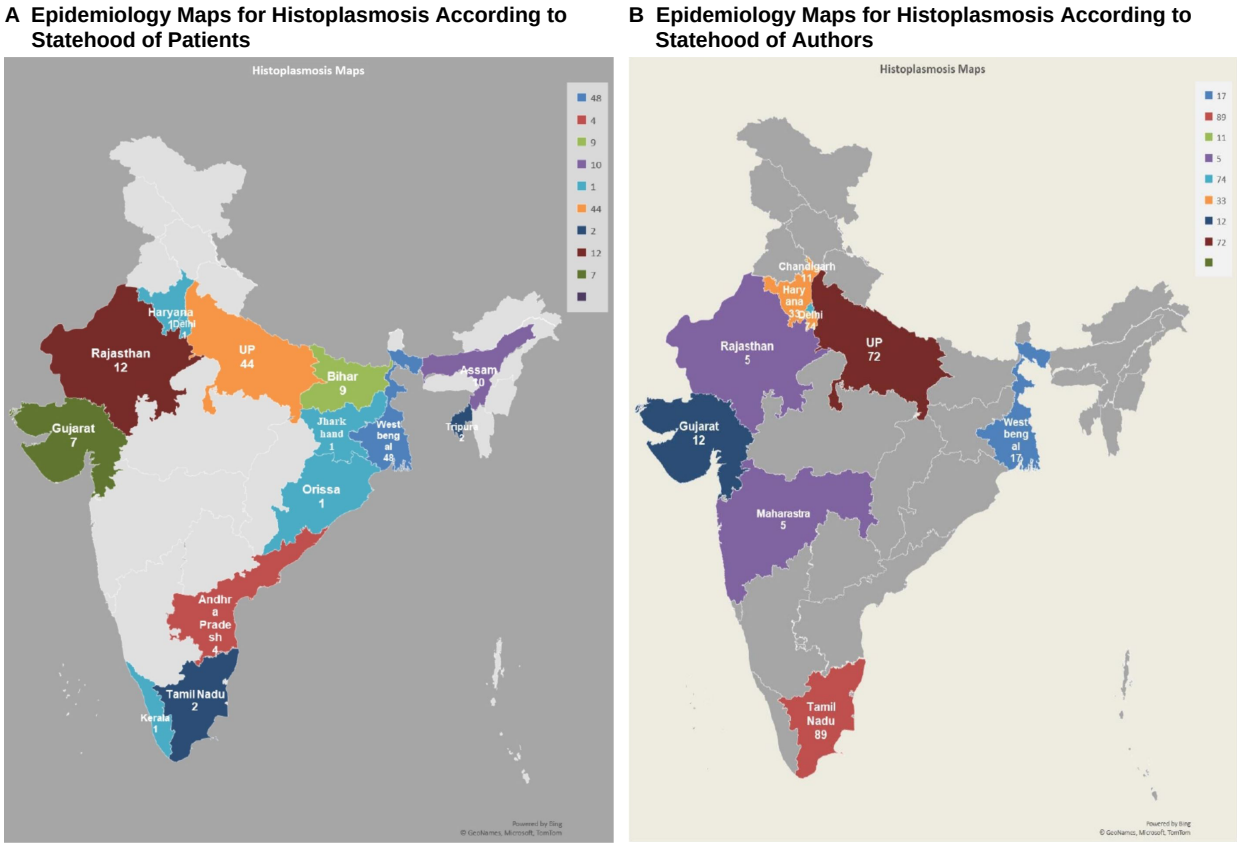

Figure 2. *A*, Published reports of histoplasmosis by state of residence of patients. *B*, Published reports of histoplasmosis according the authors' institution, by state.

beds that leads to care of critically ill patients in general wards. The total number of ward cases of candidemia (less severe) may be much higher than ICU cases as the admitted patients are mainly in wards. Similarly, our estimate of esophageal candidiasis was derived only for HIV patients, omitting all other causes, also likely an underestimate. We could not estimate the incidence of any of the clinical forms of histoplasmosis. We have ignored many patient groups at risk of IA, such as those treated with corticosteroids for autoimmune disorders, those in intensive care (without specific risk factors such as COPD, hematological malignancy, post transplant etc.), and those with severe influenza and COVID-19. The estimates for CM, ABPA, and SAFS occurring in the pediatric population could not be accounted for due to lack of relevant data.

However, it could be argued that we may have overestimated the burden of some groups of patients. Although IA burden was estimated in hematological malignancies, COPD, HIV, and transplant patients, the largest proportion was COPD patients (~90%), which is barely documented in India. Our new methodology for estimating CPA needs epidemiological validation in India. We have taken a 5% proportion of adult asthmatics as having ABPA, but on the other hand, the overall asthma prevalence was estimated at 2.9%, which could be an underestimate. Our estimate of fungal keratitis is based on data in Nepal from some years ago, which could overestimate the incidence in India. Many potential risk factors for fungal disease, such as diabetes, influenza, autoimmune conditions, burns, prolonged ICU stay, etc., were not accounted for specifically in our estimations.

Our estimate for CPA includes consideration of those misdiagnosed as tuberculosis, who had a dual infection with tuberculosis, CPA arising during anti-tuberculous treatment, as well as those (usually) left with cavitation following successful therapy to treat tuberculosis. The current estimate of incidence and 5-year prevalence is ~5 times the previous estimate [13]. This reflects the improved understanding of the etiopathogenesis of CPA as well as emerging data concerning misdiagnosed PTB, coinfections of PTB and CPA, and those developing CPA after antituberculous therapy. The lack of regular testing of patients with pulmonary tuberculosis for *Aspergillus* immunoglobulin G contributes to inaccurate diagnosis.

Our data on tinea or dermatophyte infection was intended only to capture tinea capitis. Despite multiple studies of tinea capitis, the population denominator is poor, so this estimate (25 million) is uncertain. A quiet epidemic of terbinafine-resistant tinea corporis infections caused by the newly minted fungus *Trichophyton*

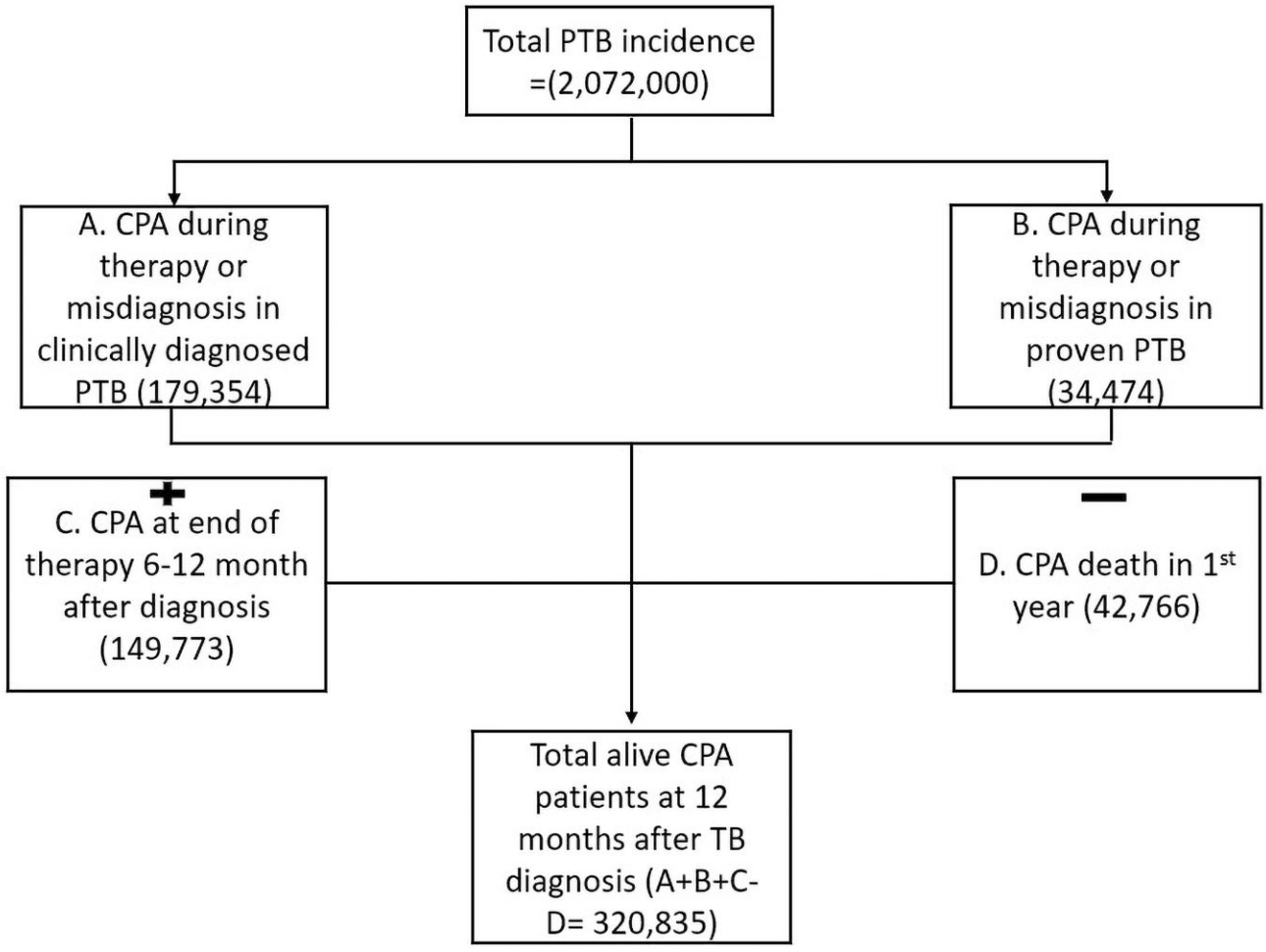

Figure 3. Figure showing the calculations involved in deriving new CPA cases (arising 12 months after TB therapy) in HIV+ & HIV- population.

indotineae is gathering pace in India and now internationally (Supplementary Data 6, ref. 28). We have not been able to estimate its prevalence.

Besides India having a very high baseline incidence of mucormycosis, the recent COVID-19 pandemic led to a massive surge of CAM cases, leading to substantial morbidity and mortality. The possible reasons suggested include excessive systemic steroids given for COVID-19 and prolonged use of masks and "repeated" nasopharyngeal swabbing, complicating newly occurring and/or uncontrolled diabetes [50, 51].

Our study has some important limitations. As country-wide data were not available for some diseases, existing data from world literature were extrapolated. Although attempts were made to report incidence data for different diseases, for many diseases only prevalence data were available, which led to inadvertent "mixing" of prevalence/incidence data at times. Some less serious fungal diseases, but important prevalent conditions including oral candidiasis, onychomycosis, and single-episode vaginal candidiasis, were not addressed in the present study. Diagnostic limitations across the country also have inhibited some high-quality epidemiological studies being done.

Nonetheless, we hope that by attempting the first comprehensive assessment of the burden of fungal diseases in India, this study will stimulate better surveillance, improve access to and use of the new generation of fungal diagnostic tests, and affect change in patient outcomes, for the better.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. A.R.: review of literature, analysis of data, projection of estimates, drafting and editing of the manuscript. A.A.: review of literature and drafting of the manuscript. S.B.: review of literature. A.C.: critical input and review of literature. D.D.: conceptualizing and designing, review of literature, analysis of data, projection of estimates, drafting and editing of the manuscript, critical input.

Patient consent. As this was a secondary review of existing literature, this manuscript does not include factors necessitating patient consent. Also, as there were no patients directly or indirectly involved in this review, no ethical clearance was deemed necessary.

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