

How Common are Fungal Diseases?

Here are summarized the key publications and reports which either define or underlie the incidence and prevalence estimates of fungal diseases worldwide. Individual country estimates are available here and in some of the global burden papers: www.gaffi.org/media/academic-papers/

Oral, oesophageal and vulvovaginal candidiasis (thrush)

- Oral thrush occurs in ~1.9 million people worldwide based on ~90% of HIV/AIDS patients¹ not receiving anti-retroviral therapy (14.6 million), estimated by UNAIDS in 2018². The number affected is probably falling as anti-retroviral therapy usage grows.
- Oral thrush also occurs in normal babies, people taking inhaled steroids for asthma, following radiotherapy to the head and neck for cancer, in denture wearers and in some leukaemia and transplant patients.
- Candida infection of the oesophagus (gullet) affects an estimated ~537,000 people as ~20% of HIV/AIDS patients³ not on anti-retroviral therapy (420,000), and ~0.5% if on antiretroviral therapy (117,000)⁴ develop it.
- Repeated attacks of vulvovaginal candidiasis affect at least 138 million women annually as 5–10% have at least 4 attacks annually^{5,6}. The 25–34 year age group has the highest prevalence (9%). An estimated 372 million women are affected by recurrent vulvovaginal candidiasis over their lifetime⁶. These estimates exclude post-menopausal women on hormone replacement therapy or diabetes. The impact of on quality of life is substantial⁷. About 70% of all premenopausal women develop thrush at some point in their lives⁸.

Invasive and life-threatening fungal infection

Candida infection

- Candidaemia occurs at a population rate of 2-26/100,000^{9,10,11}, so using 5.9 cases/100,000, ~400,000 cases are predicted worldwide, with a mortality of 30-55%¹². The numbers rose in the US by 52% between 2000 and 2005¹³, and a recent paper from the US puts annual incidence at 8.7 per 100,000 population¹⁴.). The global burden of candidaemia is therefore probably between 5 and 12/100,000 or 374,000 and 897,410 annual cases. Rates in India and Brazil are much higher¹⁵, so the overall estimate is likely to be at the top end of this range, or higher.
- Blood culture is only about 40% sensitive for detecting invasive candidiasis (including intra-abdominal candidiasis/Candida peritonitis)^{16,17} so it is likely that the annual incidence of invasive candidiasis, including intra-abdominal candidiasis, is 934,800 to 2,243,500 annual cases.
- *Candida* peritonitis (intra-abdominal candidiasis) affects both those undergoing long term peritoneal dialysis for renal failure (CAPD) and post-surgical patients, usually in intensive care. In a large multicentre

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study in 101 French intensive care units (ICU), hospital-acquired *Candida* peritonitis was documented in 73 patients over 8 months, compared with 123 patients with candidaemia without *Candida* peritonitis; 26 patients had both¹⁸. Assuming this is generalisable to other populations, this suggests a ratio of 1 patient with hospital-acquired (almost all post-operative) *Candida* peritonitis for every 2 patients with candidaemia, in ICU. As between 30 and 50% of candidaemia cases occur in ICU, and there are about 400,000 episodes of candidaemia globally, this suggests about 60,000 - 100,000 cases of *Candida* peritonitis each year. The mortality of *Candida* peritonitis was 38%. In those with end stage renal disease worldwide (~1.7M) CAPD is used in about 50%. Patients get 1 infection per 18 months on average¹⁹ and ~0.05 episodes per patient year are attributable to *Candida* spp., equivalent to ~42,500 cases annually. The mortality is 15-20%^{20,21} although survivors almost all have to transfer to haemodialysis.

- Around 150,000 of the 7.5 million patients admitted to intensive care (ICU) in Europe, USA and Japan each year grow *Candida* in their urine (a rate of 2.7% of ICU admissions²²) and is a common finding in hospitalised patients²³ and those with catheters (~16%)²⁴ especially those in ICU.

Invasive aspergillosis

- Over 10 million patients in Europe, USA and Japan are at risk of invasive aspergillosis (IA) each year because of leukemia, lymphoma, transplantation, severe illness, COPD and corticosteroid or other therapies, and often a combination of these factors. Over 50% of patients with IA die, even with treatment.
- Over 350,000 patients develop IA annually. Key groups include 3-13% risk in leukaemia (437,000 new cases annually)²⁵ (~30,000 IA cases) and 10% rate in stem cell and other transplants (>75,000 annually in the USA, Europe and Japan) (7,500 IA cases) and 1.3-3.9% of COPD patients admitted to hospital^{26,27,28}.
- A recent re-estimation of the prevalence of GOLD stage II-IV COPD found over 550 million of whom a conservative number (58 million (10.5%) annually) are admitted to hospital²⁹. Of these admissions, 753,073 (1.3%) - 2,272,322 (3.9%) develop IA and 540,451-977,082 deaths are predicted annually. A mean rate of COPD admissions in OECD countries of 198/100,000 (range 364 (Ireland) to 71 (Portugal))³⁰.
- IA also complicates lung cancer, at a rate of 2.63%³¹. Worldwide there are 2 million lung cancer cases annually²⁴, consistent with an additional 52,600 IA cases. A recent large survey of IA in liver failure in China documented a 5% rate, with a 95% mortality³². IA complicated 19% of patients with severe influenza with an overall mortality of 45%, and an attributable mortality of 25%, even diagnosed and treated rapidly³³. IA also complicates Covid pneumonia at a rate of ~20% if severely ill^{34,35}. All these patient groups above probably account for

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90% of IA patients, with those admitted to intense care (ICU), with lymphoma or chronic leukaemia and various immunological disorders and treatments accounting for the remainder. IA occurring in ICU is probably commoner than realized with a baseline rate of 5% not including influenza³³, but may be higher – 12% in a recent multi-centre study, in which IA was actively sought with bronchoscopy culture and *Aspergillus* antigen³⁶. Under diagnosis is a major problem in this disease.

Cryptococcal meningitis

- The incidence of cryptococcal meningitis in AIDS estimates 223,100 cases in AIDS, using 2014 data³⁷. Deaths are high, because of a lack of diagnostic capability and optimal treatment and thought to be about 181,100, 15% of all AIDS deaths³⁷. In addition, cases occur in other immunocompromised groups and in normal people. In Thailand the records are good, and an estimated 108 'normal' and 251 immunocompromised people develop cryptococcal meningitis each year³⁸.

Pneumocystis pneumonia

- About 2 million HIV/AIDS infected patients² who should be receiving anti-retroviral therapy are at risk of *Pneumocystis pneumonia* (PCP), as well as many other immunocompromised patients, unless taking oral antifungal prophylaxis with cotrimoxazole.
- The rate of PCP as an AIDS indicator disease is very variable. In African children, using reasonably sensitive diagnostic methods prevalence rates were 10% (South Africa, 2000), 49% (South Africa, 2002), 31% (Botswana, 2003) and 5% (Malawi, 2011). In adults from Africa, rates were 9% (Malawi, 2001), 33% (Tunisia, 2002), 37% (Kenya, 2003), 11% (Malawi, 2007), 30% (Ethiopia, 2008), 4% (Uganda, 2010), 5% (Namibia, 2012), 10% (Tanzania, 2012) and 11% (Uganda, 2012)³⁹. Patient inclusion varied in these studies. *Pneumocystis pneumonia* has a 10-30% mortality in the USA and UK^{40,41}.
- Precise estimates of annual incidence are difficult because of diagnostic deficiencies but case numbers certainly exceed 400,000 globally per year⁴².
- Given the number of other patients at risk for *Pneumocystis pneumonia* and rising rates in the UK⁴³ and elsewhere in non-AIDS patients, a rough estimate of 100,000 additional cases per year is estimated³⁷.

Histoplasmosis

- In AIDS, disseminated histoplasmosis is a devastating infection and difficult to diagnose rapidly enough to save the patients, even with either rapid antigen or PCR testing. As the rates are highly variable from one locality to another, a global burden estimate is missing. An approximation of ~100,000 is likely⁴⁴, with Central and parts of South

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America most affected, and some cases in Africa and SE Asia. A recent paper estimated 6,710 to 15,657 cases of AIDS-associated disseminated histoplasmosis in 2012 in Latin America⁴⁵.

- Up to 50 million people are thought to have been infected with histoplasmosis, with ~500,000 new infections each year, most asymptomatic and based on skin testing⁴⁶. About 25,000 cases of symptomatic histoplasmosis are estimated in the USA annually¹⁴.
- Chronic pulmonary and subacute disseminated histoplasmosis are grossly under diagnosed and there are no prevalence figures published.
- Histoplasmosis caused by *Histoplasma capsulatum* var. *dubosii* (so called African Histoplasmosis) appears to be rare and there are no estimates of its prevalence⁴⁷.

Mucormycosis

- Population estimates of mucormycosis in most countries vary from 0.6-3 per million^{48,49,50}. The high rate of diabetes in India is probably partly accountable for a much higher rate of mucormycosis there, as well as unique presentations such as renal mucormycosis; the projected annual incidence is as high as 14 per 100,000⁵¹. No global estimate is available.

Coccidioidomycosis

- About 150,000 cases of coccidioidomycosis occur in the US each year⁵². In Mexico, about 8,552 symptomatic cases are thought to occur (7.6/100,000), but exposure based on skin testing is about 6 times higher than this at 43/100,000⁵³. Many more cases occur in other countries in Central and South America, but there are no good estimates.

Talaromycosis (infection with *Talaromyces marneffeii*)

- *Talaromyces marneffeii* (previously *Penicillium marneffeii*) is a potentially life threatening endemic opportunistic fungal infection, primarily reported in HIV patients living in north eastern states of India, Thailand, southern provinces of China, Taiwan, Philippines, Malaysia, New Guinea, Indonesia, Cambodia, Laos, Myanmar and Vietnam. It is likely that there at least 10,000 cases annually in AIDS, but data are scanty¹².

Allergic fungal disease

Allergic bronchopulmonary aspergillosis (ABPA)

- Approximately 4.8 million people develop ABPA among the 193 million adults with active asthma worldwide⁵⁴. This assumes that ~2.5% (0.7-3.5%) of adults referred to a specialist over 1-4 years have ABPA (6 studies from Ireland, New Zealand, China, Saudi Arabia and South Africa) and this represents the whole community of asthmatics. It could both under- and over-estimate prevalence. It is likely an

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- under-estimate for India where this disease is more common⁵⁵ and distinctive for the frequency of hyper-attenuated mucus on CT scan⁵⁶.
- Individual country estimates of asthma prevalence in adults for 70 countries from 2012 are published⁵⁷, and many other countries have more recent or different statistics.
 - ABPA also occurs in children with individual cases described and several series from India^{58,59}. In children in India with 'perennial' asthma or 'poorly controlled' asthma, prevalences of 15% and 26% were reported^{60,61}, with an estimate for all children with asthma of 6.5%⁵⁵.
 - ~ 15% of adults with cystic fibrosis develop ABPA with ~6,675 affected, although many teenagers and some younger children are also affected⁶².

Severe Asthma with Fungal Sensitisation (SAFS)

- Fungal sensitization (allergy) is common in asthma and increasingly common in severe and poorly controlled asthma. Severe Asthma with Fungal Sensitisation (SAFS) is predicted to affect ~6.5 million (range 3.25-13 million) adults worldwide depending on the frequency of severe asthma (5-20% of all asthmatics)^{12,63}. There is some duplication between ABPA and SAFS (collectively termed 'fungal asthma') because all ABPA patients are sensitized to fungi, and some have severe asthma.
- SAFS probably occurs in children but is poorly documented. In India 17% of 100 children with persistent asthma were sensitised to fungi and 60% of those with severe asthma⁶⁴. One cross-sectional study from Russia found 30% of 120 children with poorly controlled asthma to be sensitized to *A. fumigatus*⁶⁵.

Allergic fungal rhinosinusitis

- A rough estimate of the point prevalence of fungal rhinosinusitis (FRS) is derived from a study in north India - 1.4% adults suffer from chronic rhinosinusitis (which translates globally into 73 million), of whom 8.1% of them have fungal rhinosinusitis or ~6 million adults⁶⁶. The disease distribution in this study was: allergic FRS in 41 (56.1%), chronic granulomatous FRS in 13 (17.8%), eosinophilic FRS in 11 (15.0%), fungal ball in 7 (9.5%) and chronic invasive FRS in one (1.3%). In Israel, nearly 0.5% of the population (40,000) is thought to be affected by FRS⁶⁷. Amongst patients who undergo endoscopic sinus surgery for all reasons, 6.8% (in Brazil) have allergic FRS⁶⁸.

Chronic fungal disease of the lower and upper respiratory tract

- Prevalence of chronic pulmonary aspergillosis following tuberculosis is estimated at about 1.2 million cases⁶⁹. A prospective cross-sectional study in northern Uganda found the annual rate of new CPA development between surveys 2 years apart was 6.5% in those with

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chest radiography cavitation and 0.2% in those without⁷⁰. Chest radiographs after tuberculosis treatment reveal cavitation in 20–30%. Each year, ~7.7 million patients are cured of pulmonary TB and so using the rates from Uganda with and without residual cavitation, then 112,000–160,000 people will develop CPA worldwide every year, a lower rate than previously suggested. However incomplete data on prevalence at the end of 6 months of TB therapy, are indicative of ~9% having CPA in Uganda⁷¹ and a similar number in Indonesia⁷², Rates are particularly high in smear and/or GeneXpert negative (ie clinically diagnosed) non-HIV patients (22%), but HIV positive patients may also be affected⁷³.

- Chronic pulmonary aspergillosis complicates many respiratory disorders including tuberculosis, ABPA, sarcoidosis and COPD^{16,74,75}, and so the total burden of this debilitating disorder is ~3 million³⁷.
- *Aspergillus* bronchitis affects primarily those with bronchiectasis and cystic fibrosis. One cross-sectional study found ~30% of adults with cystic fibrosis to have *Aspergillus* bronchitis⁷⁶, which translates into 11,300 affected, not including India and some other countries⁵⁷.
- Chronic and granulomatous FRS are uncommon subacute entities, only found in adults. In the community survey in India, chronic granulomatous FRS was found in 13 (17.8%) and chronic invasive FRS in one (1.3%), which translates to a point prevalence in India of 1.5% of the 1.4% with any form of FRS, so ~0.02% of the adult population – 182,000 affected. These diseases are more common in the Indian sub-continent and Middle East, but other estimates are lacking.

Neglected Fungal Tropical Diseases of the skin

- There are no global estimates for the Neglected Fungal Disease mycetoma⁷⁷. A 2013 survey reported a total of 8,763 cases of mycetoma⁷⁸. A WHO survey expanded the number of countries ever reporting mycetoma cases and in Africa, Eastern Mediterranean Region and the Americas, in 2016 840 new mycetoma cases were reported. A recent revision found 19,494 cases dating from 1876 to 2019, and new geographical loci, including the United States, Venezuela, Italy, China, and Australia⁷⁹, including multi-year series from Senegal and Uganda^{80,81}. Most cases were reported from Sudan, Senegal and El Salvador. This total is certainly a substantial underestimate the annual incidence.
- The prevalence of chromoblastomycosis⁶⁹ varies from 14/100,000 in Madagascar (3,500) to 3/100,000 (6,200) in Brazil and fewer elsewhere⁸². From other countries, Mexico, Dominican Republic, Venezuela, India, Taiwan and Southern China have the majority of reported cases.
- Sporotrichosis⁶⁹ is probably more common but very variable in frequency with hyper-endemic areas in Mexico and Peru with rates as

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high as 25/1,000⁸³. There are fewer data on other similar conditions such as cutaneous phaeohyphomycosis.

Fungal eye infections

- Estimates of the annual incidence of fungal keratitis vary from 1 million to 1.4 million⁸⁴. Rates vary from as low as 0.02/100,000 in Europe to as high as 73/100,000 in Kathmandu⁸⁵. Rates in Nepal have fallen in recent years to 73/100,000 (20,000 affected)⁸⁶. The incidence of fungal keratitis in S. America was found to be 5/100,000 in Colombia⁸⁷. The annual incidence in Africa is not known, but may be ~13.5/100,000. Among causes of avoidable blindness, corneal opacities (caused by fungi or bacteria) accounts for 10% of the 284 million people visually impaired worldwide⁸⁸.

Cutaneous fungal infections

- Fungal infection of the skin, hair or nails affects ~1 billion people⁸⁹ and in the US alone accounted for 4M outpatient medical visits⁹⁰.
- Fungal nail infection (onychomycosis) is common in the general adult population, probably 5-25% rate with an increasing incidence in elderly people^{91,92}.
- Athlete's foot (tinea pedis) is more common than onychomycosis and is more common in younger people and sportsmen.
- Hair infection (tinea capitis) is most common among children, often resulting in bald patches with psychosocial consequences. In a recent US survey, tinea capitis was found in 6.6% with ranges from 0% to 19.4%⁹³, is more common in deprived areas and black children (with rates up to 41%)^{94,95,96,97}, suggesting a global prevalence of 200 million cases.

A summary table is shown below:

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Infection	Global burden estimates in main underlying disease groups				
	None	HIV/AIDS	Respiratory	Immune deficit	Critical care
Life-threatening infections					
Invasive aspergillosis			>750,000	>40,000	>250,000
Candida bloodstream infection	50,000			600,000	300,000
Candida peritonitis (intra-abdominal)				42,500	>60,000
Cryptococcal meningitis	10,000's	223,000		10,000's	
Pneumocystis pneumonia		~400,000		>100,000	
Histoplasmosis	>25,000	>25,000	?10,000	>10,000	
Coccidioidomycosis	~150,000	>500		5,000	
Mucormycosis	>5,000			>150,000	>5,000
Talaromycosis (<i>T. marneffei</i> infection)		>10,000			
Superficial fungal infections					
Oral thrush		1,900,000	100,000's	millions	
Oesophageal candidiasis		537,000		>100,000	
Recurrent Candida vaginitis	~138,000,000				
Candiduria				>200,000	>150,000
Fungal hair infection	200,000,000				
Onychomycosis, ringworm, tinea pedis and other skin fungal infections	>700 million	10,000,000			
Chronic fungal infections					
Chronic pulmonary aspergillosis			3,000,000		
Aspergillus bronchitis			>20,000		
Chronic invasive/granulomatous fungal rhinosinusitis	>200,000				
Paracoccidioidomycosis	~2500				
Allergic fungal infections					
ABPA in asthma and cystic fibrosis			4,800,000		
Severe asthma with fungal sensitisation			>6,500,000		
Fungal rhinosinusitis	~6,000,000				
Fungal NTDs					
Fungal keratitis	>1,000,000				
Sporotrichosis	>40,000				
Mycetoma	>20,000				
Chromoblastomycosis	>25,000				
Totals	>1,044,002,500	~13,095,500	>15,000,000	>2,000,000	>760,000

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