95/95 BY 2025

ENSURE THAT BY 2025 95% OF PEOPLE WITH SERIOUS FUNGAL DISEASE ARE DIAGNOSED AND 95% TREATED = 95-95

Appendix 3

Burden of Fungal Diseases

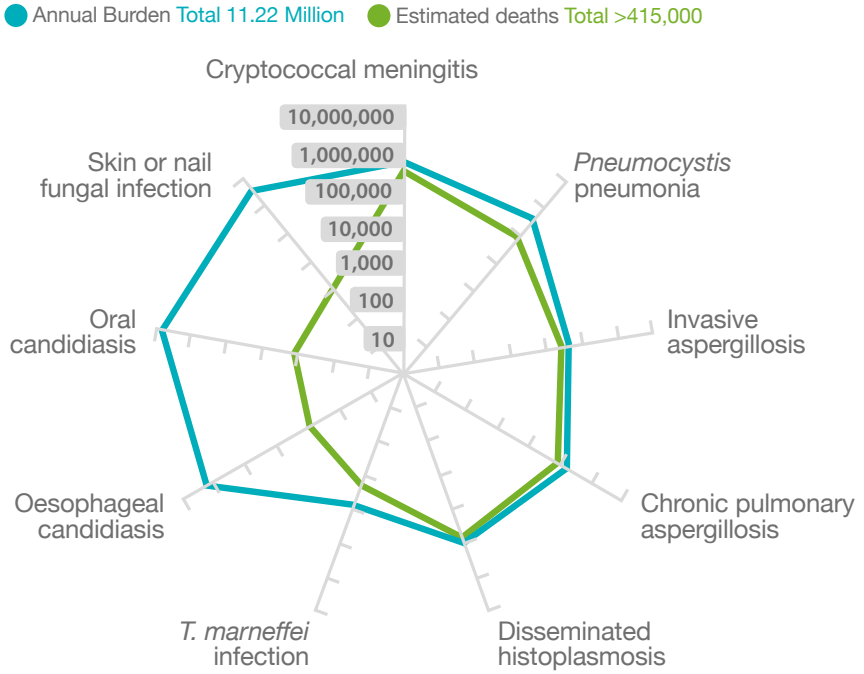
About 30 fungal species cause 99% of human fungal disease burden. In decreasing frequency, these diseases are cutaneous (skin hair and nails) fungal diseases, mucosal candidiasis, allergic fungal conditions usually complicating asthma, chronic skin, lung, sinus and bone infections, and the acute life or sight-threatening fungal infections. The vast majority of infections are globally distributed, though a few are specific to continents, tropical zones or even localized regions. There are exceptionally few studies precisely documenting the number of infections, but many studies attest to the mortality impact of the most severe infections.

3A. Major AIDS-associated fungal infections and their impact

Collectively, fungal infections are by far the most common infections in AIDS.

Oral and oesophageal candidiasis are extremely common, and worldwide (Figure 3.1). Point prevalence surveys of oral candidiasis in unselected HIV clinics regularly identify 50% affected, consistent with annual rates of ~90% in those with low CD4 cell counts (37). In such settings, oral and oesophageal thrush remains a hallmark for AIDS. Rates of oesophageal candidiasis in those presenting with AIDS are ~22% (38), falling to ~5% of those on ARVs (39).

Figure 3.1 Spider diagram of the burden and deaths from the most frequent fungal infections in HIV/AIDS patients.



'Implementation science projects are crucial steps to improving care and patient outcomes across the world. CDC and PEPFAR have joined forces in assessing cryptococcal screening strategies at the start of antiretroviral therapy in Uganda, Zimbabwe and Vietnam.'

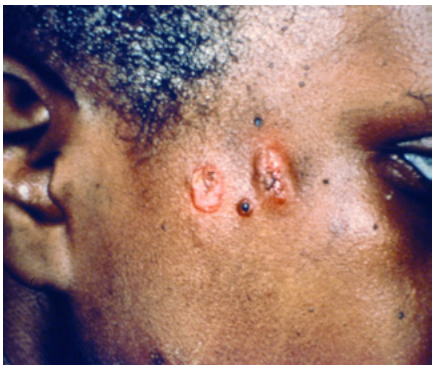
Dr Jonathan Kaplan
Division of Global HIV/AIDS, Centers for Disease Control, Atlanta, USA

References numbered in the text can be found in **Appendix 8**

Burden of Fungal Diseases

Pneumocystis pneumonia (PCP) is a relatively common AIDS-defining illness which occurs worldwide and is transmissible from person to person. It varies in incidence, but is a cause of death in a significant minority of patients sampled at autopsy. Virtually all patients with PCP who are not treated die. Late diagnosis has a worse outcome, and mild cases can be treated with oral therapy as an outpatient, without hospital admission.

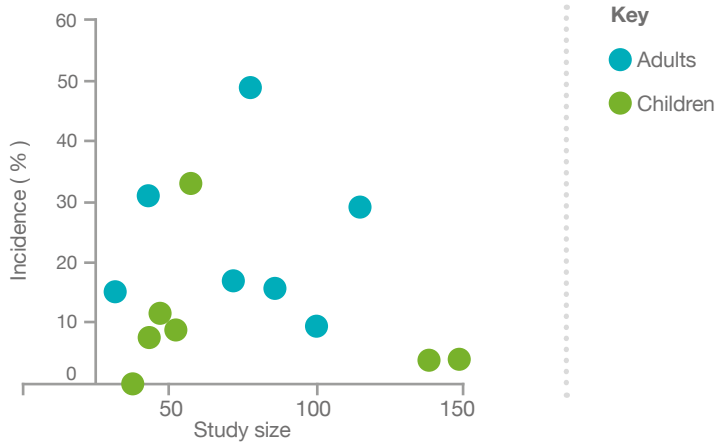
It is not known how many patients with AIDS develop PCP. The chart below (Figure 3.2) shows the relative frequency of PCP among AIDS patients in different studies (details can be found on GAFFI's website.) In Africa, the frequency of PCP in AIDS varies substantially, probably in part because of the accuracy of diagnosis and 'competing' infections such as TB and pneumococcal pneumonia. Among those with <100 CD4 cells, a low median estimate from Thailand was 14.7% (36), which extrapolated worldwide would result in an estimated 400,000 patients affected. In fact those with CD4 cells between 100 and 200 are also at risk for PCP, so 400,000 cases is likely to be a low estimate of burden.



Above. Cutaneous ulcers of disseminated cryptococcal disease, without meningitis, both unusual features.

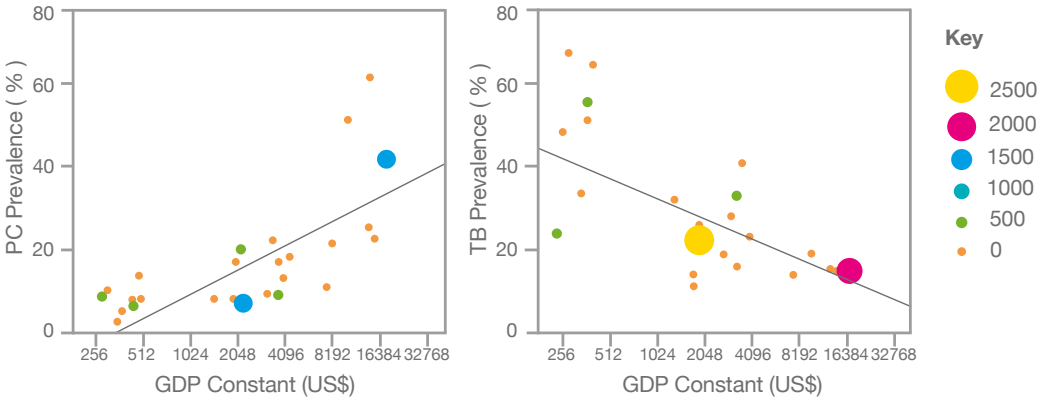
DEATHS from fungal infections in AIDS are estimated at 700,000 annually, nearly half the total. Concrete steps to improve diagnosis and access to therapy, including a screen and treat program for pre-symptomatic cryptococcal, disease, could realistically reduce deaths by 457,000 by 2020, if 60-90% of patients are reached.

Figure 3.2 Incidence of PCP in adults and children with HIV infection from different studies.



There is also a relationship between rising GDP and increasing rates of PCP (40). As TB rates fall, so PCP rates rise (Figure 3.3). The reasons for this are not clear, but could reflect competing causes of initial illness, more advanced therapies, such as cancer chemotherapy, opening up additional risk groups for infection, or better documentation

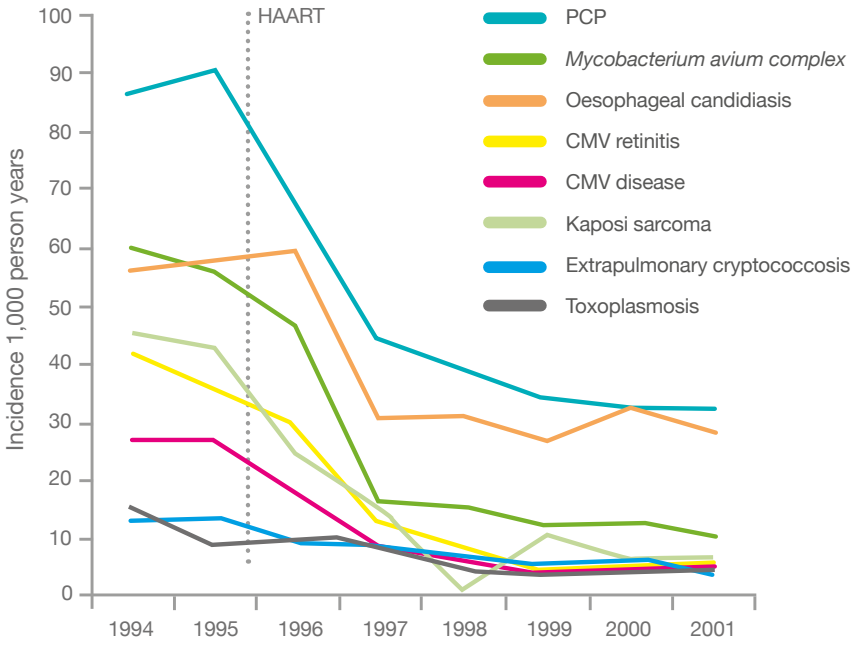
Figure 3.3 Relation between GDP and PCP and TB incidence in HIV patients compared (16).



Burden of Fungal Diseases

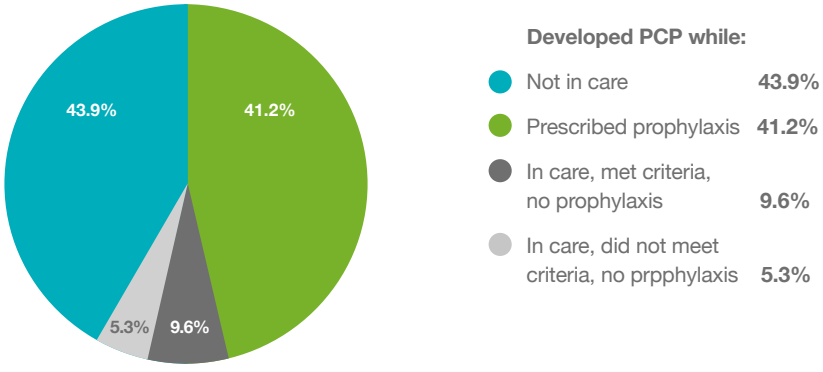
The introduction of ARVs has substantially reduced the frequency of most fungal infections, but nowhere near close to zero. In the USA to 2001, after widespread introduction of ARV therapy, falls in fungal infections were seen, but there was a substantial residual burden of PCP and oesophageal candidiasis (Figure 3.4) (41). About half the patients developing PCP were under care and 'prescribed' prophylaxis (Figure 3.5) (41).

Figure 3.4 Falls in the incidence of several opportunistic infections in AIDS in the USA over time as ARVs are increasingly prescribed.



Diagnosis of PCP is mostly empirical with characteristic infiltrates and low oxygen levels, but the presentation is often atypical. Assuming that 50% of patients are treated currently and 70% of them survive currently, the existing annual mortality from PCP is ~260,000. If better diagnosis is instituted, with good clinical guidelines, the diagnosis rate should rise to 80% with only a 20% mortality, saving 120,000 lives annually. The incidence of PCP is likely to fall as 90-90-90 rolls out, yet better diagnosis and treatment in parallel is critical, as breakthrough occurs. There are other arguments for improving the diagnostic approach to PCP (Appendix 7/5).

Figure 3.5 PCP occurring in the USA in HIV patients depicted by prophylaxis status.



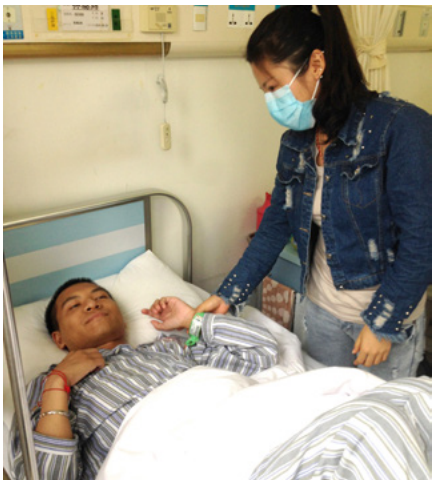
'Sensitive PCR-based methods for *Pneumocystis* detection are unavailable in resource-limited settings. Sputum microscopy would be easier to implement than PCR, but its sensitivity for *Pneumocystis* detection is lower than that of PCR.'

Dr Carlos Fritzsche
University of Rostock, Dept. of Tropical Medicine and Infectious Diseases

Burden of Fungal Diseases

Cryptococcal meningitis

Cryptococcal meningitis varies substantially in frequency in AIDS, but also occurs in non-AIDS immunocompetent patients The CDC estimated the burden of cryptococcal meningitis in AIDS using regional or continental rates and existing HIV estimates in 2007 (1). The most conservative estimate for AIDS-related cryptococcal meningitis cases worldwide was 372,000 and additional modeling work in progress suggests the total could be 240,000, and accounts for about 11.6% of all AIDS mortality (42). Currently the ten-week survival in treated cases is 30-50%. Since many patients are never diagnosed, it is likely that 160,000 to 250,000 AIDS deaths are attributable to cryptococcal meningitis. Rates fall dramatically with ARV therapy, although still occur because of poor compliance and virological failure. Cases also occur in the first year of ARVs, with a high mortality (11-15), and patients with occult cryptococcal disease who start ARVs without treatment of cryptococcal infection being treated have a higher mortality than those whose ART is delayed.



Above. 25 year old previously normal student, left blind and deaf from cryptococcal meningitis, being visited by his girlfriend.

Cryptococcal antigenaemia and meningitis varies substantially in frequency in AIDS, with rates varying by country and sometimes within country. So countries with documented high rates of cryptococccal antigenaemia (ie 10-13%) include Cambodia, Cameroon, Ethiopia, Guniea-Bissau, Nigeria and Thailand, with intermediate rates (4-10%) include Argentina, Colombia, Indonesia, Kenya, Rwanda, South Africa, Tanzania, Uganda, United Kingdom and Vietnam) and low (under 4%) include Brazil, Cote d'Ivoire, Gabon, Ghana, Malawi, Mali, Peru, Togo and USA.

Cryptococcal pneumonia and meningitis also occurs in non-AIDS immunocompetent patients. Rates in non-AIDS patients exceed those in AIDS in China and most of Europe but not Thailand or most of Africa and the Americas (see Table 3.1). No global burden of cryptococcal disease in non-AIDS patients has been attempted.

Table 3.1 Estimates of the relative numbers of patients with cryptococcal meningitis by underlying disease in China and Thailand - selected examples

Country	Non-immuno-compromised	HIV/AIDS	Non-HIV immuno-compromised	Totals
China	922 (40%)	461 (20%)	922 (40%)	2,305
Thailand	108 (3.9%)	2,389 (87%)	251 (9.1%)	2,747

Histoplasmosis

Disseminated histoplasmosis is common as an AIDS-defining illness in Central and South America, with a mortality ~50%, if the diagnosis is not made immediately. The rate of disease does not fall with ART rollout, probably because *Histoplasma* is a primary pathogen. Either urinary antigen or blood PCR are excellent early diagnostic tools but they are available in only a few centers. Mortality can be reduced from over 50% if based on culture, to less than 20% with PCR or antigen diagnosis, if treated.

In highly endemic regions of the Americas, histoplasmosis is more common than TB as a presenting feature of AIDS (43). Confusingly, TB is also a common concomitant infection. In low endemicity areas, such as northern Tanzania, rates are ~1% of newly hospitalized AIDS patients (44). The frequency of histoplasmosis exceeds that of tuberculosis as the CD4 count falls in the highly endemic country French Guinea. (Figure 3.6)

Burden of Fungal Diseases

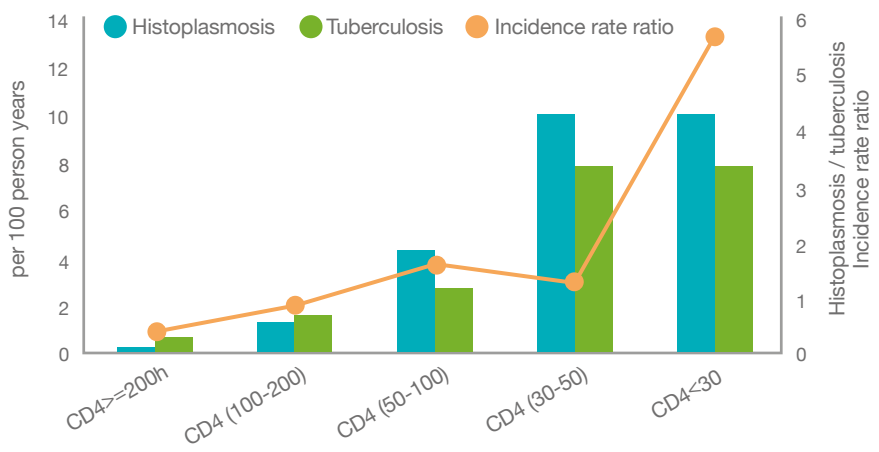
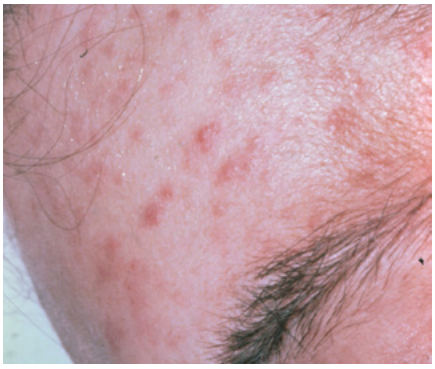


Figure 3.6 Relative rates of disseminated histoplasmosis and TB at different CD4 strata in HIV infection.

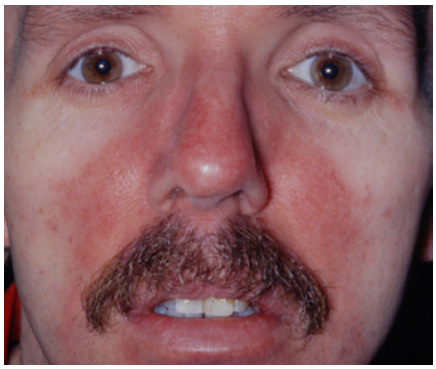


Above. Typical example of the rash of disseminated histoplasmosis in AIDS, which unfortunately for diagnostic purposes is uncommon.

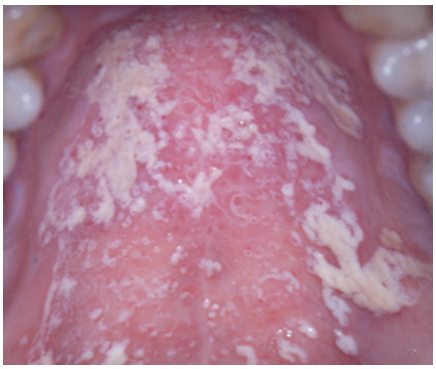
The global number of disseminated histoplasmosis (DH) cases in AIDS has been provisionally estimated to be between 100,000 and 300,000 annually (45). Improved outcomes with early diagnosis and appropriate therapy can achieve 85% survival. Using the most conservative estimate of 100,000 cases, and assuming that only 20% of patients currently have access to rapid diagnosis, then about 80,000 annual deaths are anticipated.

Other fungal infections in HIV/AIDS patients

The global burden of oral and oesophageal candidiasis, *T. marneffei* infection, cutaneous infection including onychomycosis have been roughly estimated (3) and are depicted in figure 3.1. Skin fungal infections affect a billion people worldwide, and are especially problematic in HIV-infected people (7). Most are transmissible from person to person. The commonest infections are tinea capitis (hair infection), onychomycosis (nail infection) and ringworm and other skin infections. While most of these are unsightly and impinge on quality of life, some lead to significant consequences. Severe and distinctive onychomycosis is an early feature of HIV infection.



Above. An example of severe seborrhoeic dermatitis in an HIV positive patient, requiring oral antifungal therapy with itraconazole.



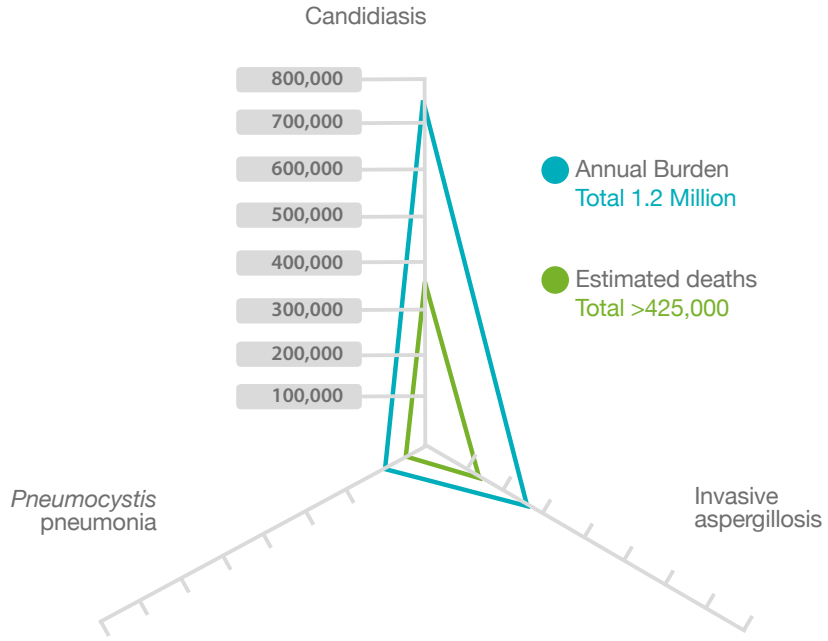
Above. Severe candidiasis on the palate in AIDS, caused by a fluconazole resistant strain.

Above. Doctor in Kampala doing a lumbar puncture in an AIDS patient with suspected cryptococcal meningitis. (Thanks to David Boulware)

Burden of Fungal Diseases

3B. Hospital-associated infection in cancer, transplant and intensive care

For the hospitalized patient, the most common life-threatening infections are candidaemia/invasive candidiasis and invasive aspergillosis. Very approximate global annual incidence figures are shown in Figure 3.7.



'Early treatment of fungal infections decreases costs by shortening hospital stays and decreasing comorbidities, as well as saving lives.'

Blanca Samayoa
Asociación de Salud Integral, Guatemala

Figure 3.7 Spider diagram illustrating the estimated burdens of the commonest 3 infections in hospitalised and critical care patients. Invasive aspergillosis estimate is probably a significant under-estimate.

Invasive candidiasis

Candida bloodstream infection (candidaemia) is one manifestation of invasive candida infection, and is found in about 40% of invasive candidiasis cases. Population rates of candidaemia vary from as low as 2 per 100,000 to 26 per 100,000. Using a low average rate of 5/100,000 (46) and a global population of 7 billion, 350,000 candidaemia and 875,000 invasive candidiasis cases are estimated. In intensive care, the incidence of candidaemia is much higher at 0.24 to 34.3 patients/1,000 ICU admissions and in India, 6.5/1,000 ICU admissions (47). These data indicate that the total caseload of invasive candidiasis in India is likely to be as 675,710 per year with an estimated mortality of 50% leading to 337,855 deaths. Rates are rising in France (48,49) and the mortality remains stubbornly above 50% (Figure 3.8); in India the 30-day crude and attributable mortality rates were 45% and 20% respectively (47).

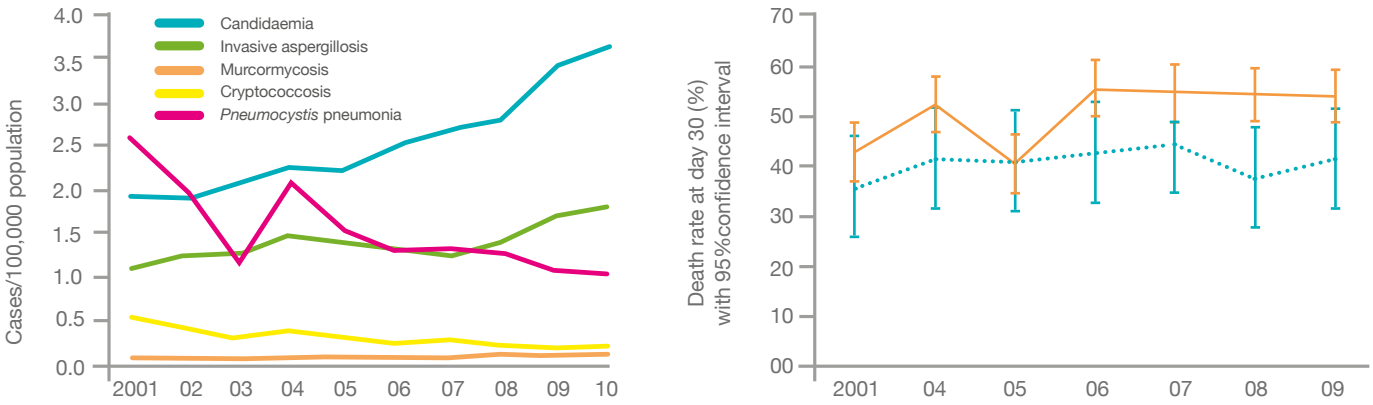
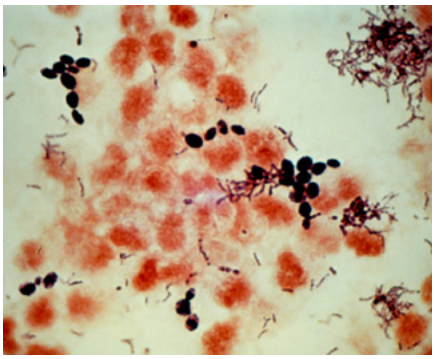


Figure 3.8 Rates of invasive fungal infections in France over time (left panel) (45) and mortality from *Candida* bloodstream infection in Paris (46).

Burden of Fungal Diseases

Several species of *Candida* are responsible for candidaemia and invasive candidiasis, the most common four being *Candida albicans, Candida parapsilosis, Candida tropicalis and Candida glabrata*. Candida parapsilosis infections are almost always hospital acquired and reflect poor infection control and/or contaminated intravenous solutions. Candida tropicalis infection is much more common in subtropical and tropical countries and especially invasive in leukaemia patients. *Candida glabrata* is typically fluconazole resistant and is often a breakthrough infection and is especially common in complex hospitalized patient, who are often elderly.

Delay in therapy is a common reason for poor outcomes (50), as is incorrect initial therapy (48). Molecular assays are potentially faster, but not fully commercialized and a survival benefit for their use and the impact of slow or fast turnaround times not yet addressed. They are more sensitive however (52,53), so are potentially of great value in diagnosing invasive candidiasis, in patients with a negative blood culture. Detection of glucan in blood is an early marker of infection (53) and widely used in Japan, but the assays are not ideally suited to low volume settings. The ideal screening tool is not yet widely available, limiting the opportunity for high quality epidemiological studies.



Above. Gram stain of peritoneal exudate from a drain after major intra-abdomial surgery, showing both multiple bacteria and yeast cells without buds or hyphae, typical of fluconazole resistant *Candida glabrata.*

Invasive aspergillosis

Invasive aspergillosis complicates cancer chemotherapy, especially leukaemia, transplantation, exacerbations of COPD and other immunosuppressed patients, including those with HIV infection (54). The timely diagnosis of invasive aspergillosis is challenging, and so a large proportion of patients are only diagnosed after death. Thus, documenting burden accurately is difficult as there is limited confidence in antemortem diagnosis in most settings. Even in high-risk patients, the diagnosis can be challenging, and many possible cases emerge. Underdiagnosis of fungal infection generally, but especially invasive aspergillosis, was well described from Italy in a large cohort of AIDS patients (Figure 3.9) (55), as in many other publications.

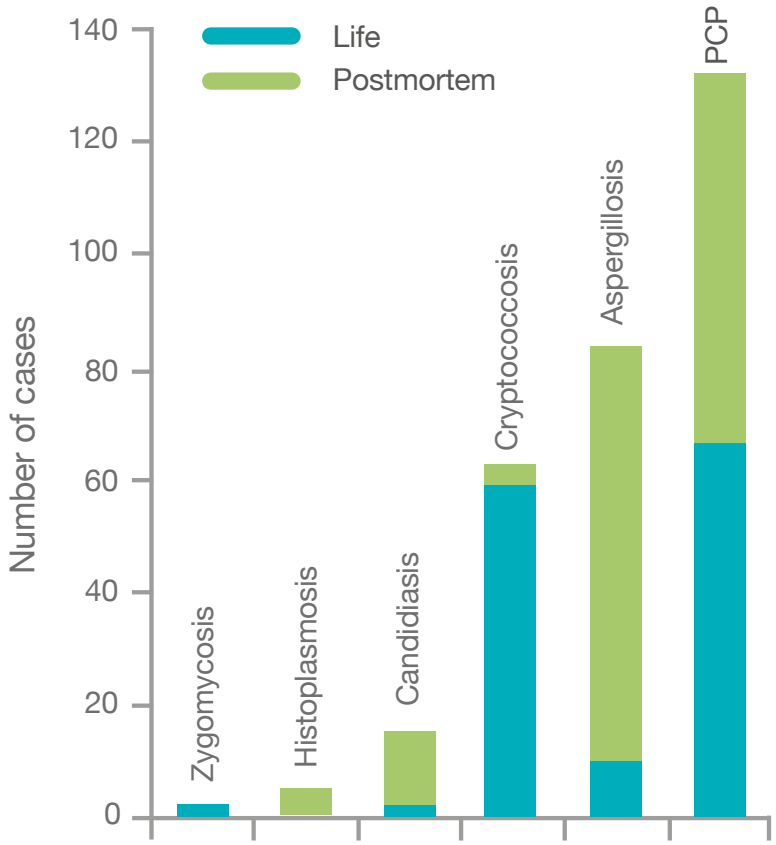
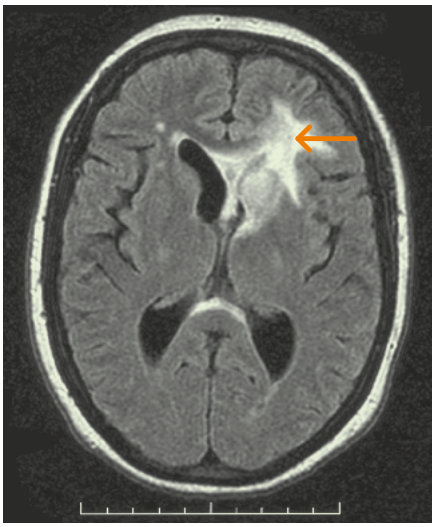


Figure 3.9 Highly variable rates of antemortem diagnosis of different fungal infections in AIDS patients in Italy, with nearly 100% for cryptococcal meningitis, about 50% for PCP and under 15% for invasive aspergillosis.

Burden of Fungal Diseases

One estimate suggested over 63,000 in Europe (population 733 million in 2010) (57). Another assessment of 200,000 patients worldwide (3) is almost certainly a substantial underestimate. The largest emerging group at risk for invasive aspergillosis is COPD patients, at least partly because they are often treated with corticosteroids. In China, 3.9% in 992 COPD patients admitted to hospital developed invasive aspergillosis (57); in Spain it was 1.3%, based on the insensitive diagnostic method – culture (58). A conservative estimate of 5% of the 65 million with COPD (56,57) are admitted to hospital annually, suggesting that over 125,000 COPD patients develop invasive aspergillosis.

Currently the mortality of invasive aspergillosis varies in different patient groups, but exceeds 99% if no treatment is given (61). With treatment, the best outcomes are in leukaemia patients, but is higher in solid organ and bone marrow transplant recipients, and very high in COPD (about 85%) and liver failure patients (>90%).



Above. Severe abscess in the brain caused by *Aspergillus* after a bone marrow transplant

Pneumocystis pneumonia in non-AIDS patients

In the UK (62), France (48) and USA (63), PCP continues to be a relatively common infection and is probably increasing in frequency (Figure 3.10). In these and other high income countries, there are more PCP cases in non-AIDS patients than AIDS patients currently, as a result of immunosuppression for cancer, chronic and autoimmune diseases.

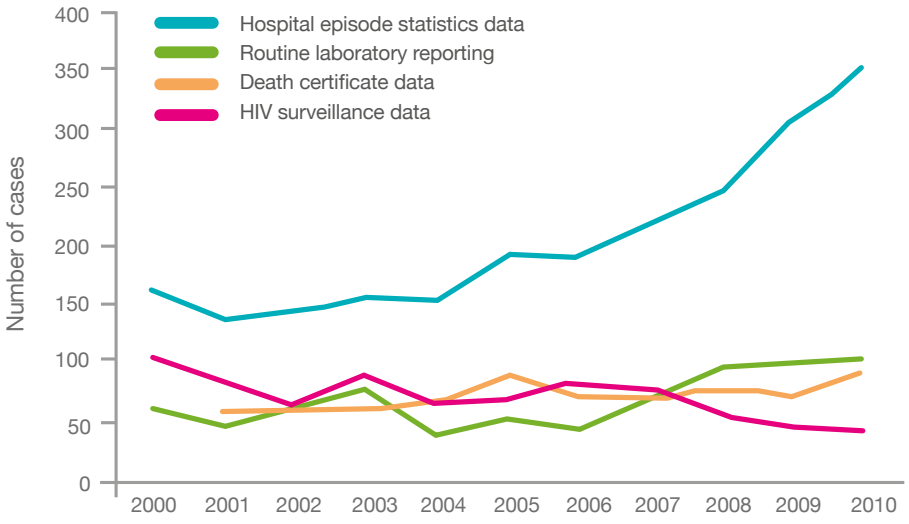
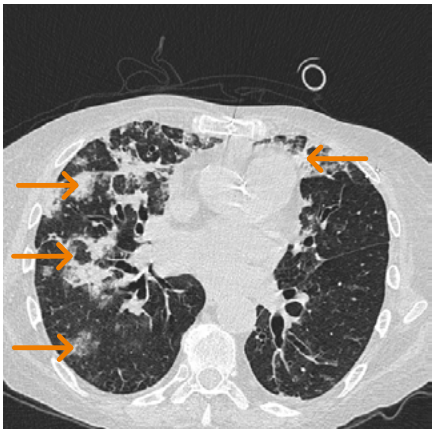


Figure 3.10 PCP in the UK, showing increasing rates, notably in non-HIV patients (62)0.



Above. CT scan showing features typical of PCP in patient without HIV, in this case high dose corticosteroids

Burden of Fungal Diseases

3C. Population (non-hospital) fungal infections of the lung and severe asthma

The lungs are a common site of fungal infection, third after skin and mucosal disease. Most infection and allergy are caused by Aspergillus spp, usually Aspergillus fumigatus. This and other rarer fungi are common in the air, breathed in daily, but fortunately do not result in illness. Allergic fungal disease is commonest in asthma, especially in adults and also in cystic fibrosis. Chronic lung infection follows an insult to the lung, notably tuberculosis. The estimated burden of these different entities is shown in Figure 3.11.

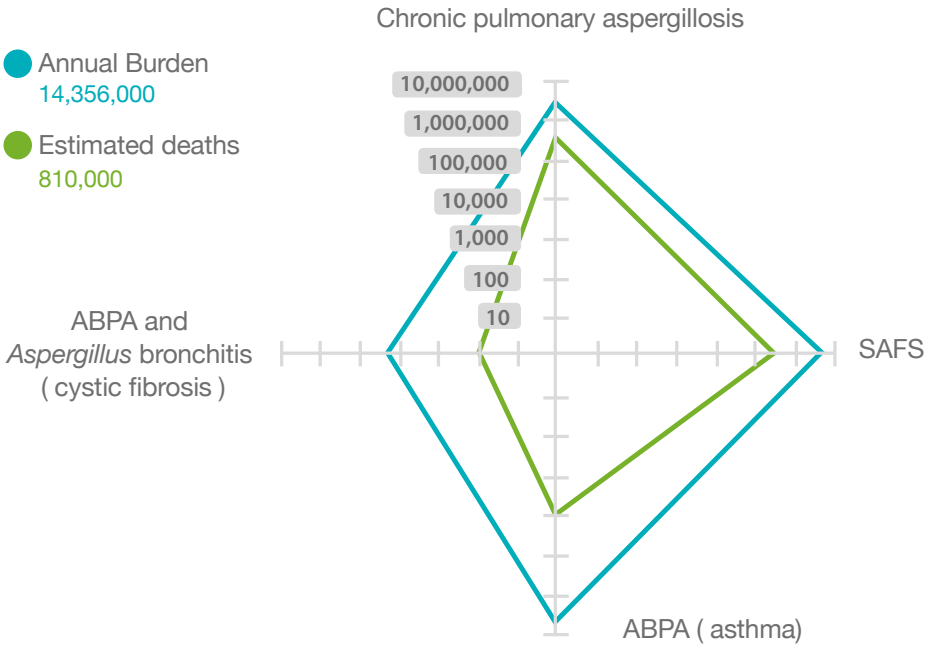
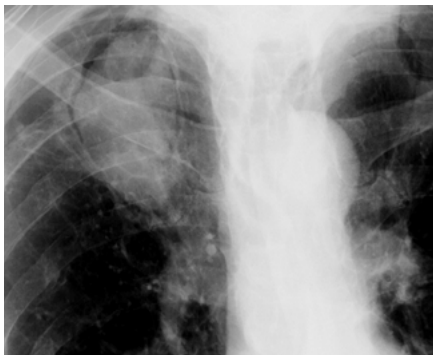


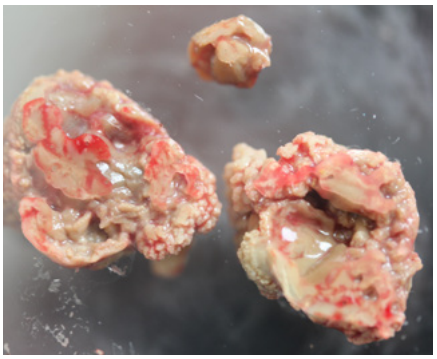
Figure 3.11 Prevalence estimates of lung diseases in the community attributable to fungal infection and allergy.

'Aspergillosis. It's actually a killer isn't it. The thought of dying of this, something you've never heard of and you're going to die of it; not a good thing at all!'

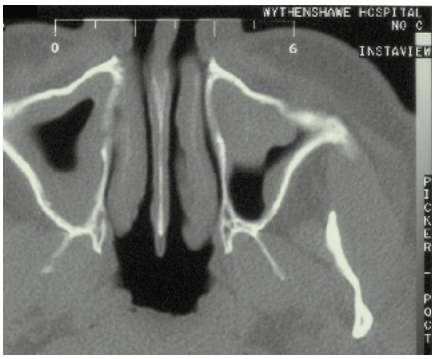
Woodrow Maitland-Brown
A patient with chronic aspergillosis



Above. Aspergilloma. Large fungal ball (aspergilloma) is a right upper lobe cavity after TB. This requires surgical removal.



Above. 3 of 10 aspergillomas removed from a patient with multiple lung cavities containing azole resistant *Aspergillus* fungal balls. The brown irregular areas are all fungus, with a small amount of (red) blood on the surface.



Above. CT scan of the sinuses showing bilateral maxillary sinusitis, with swelling of each lining of the sinuses, and probably nasal polyps on the patients left side

Burden of Fungal Diseases

Chronic pulmonary aspergillosis (CPA) is a slowly progressive lung fungal infection, which progresses to death over several years, unless arrested with treatment. Using WHO TB data, the annual incidence of CPA following TB was estimated at 375,000 and a 5 year period prevalence of 1,174,000, assuming a 15% annual mortality (2). Individual rates for the countries with populations over 50 million were also estimated (Table 3.2). Depending on the country, 20-80% of patients with CPA have TB as their underlying diagnosis, with COPD, asthma, non-tuberculous TB, sarcoidosis (5) and prior pneumothorax being others (64). A cautious estimate of 3 million people living with CPA has been proposed, based on the variable numbers of other contributing conditions.

Table 3.2 Estimated burden of CPA complicating TB in countries with a population over 50 million in 2005 (2). **DR =** Democratic republic

Country	Population (2005)	Annual pulmonary tuberculosis cases, alive at 1 year	Estimated annual CPA caseload from tuberculosis	5 year prevalence rate per 100,000 population
Global total	6,512,276,000	5,899,619	372,385	18.0
China	1,312,253,000	1,052,925	67,387	16.2
India	1,130,618,000	1,297,047	83,011	23.1
United States	302,741,000	8,907	588	0.6
Indonesia	219,210,000	420,853	26,935	38.7
Brazil	186,075,000	70,789	5,663	9.6
Pakistan	165,816,000	204,955	13,117	24.9
Bangladesh	153,122,000	243361	15,575	32.1
Russia	143,470,000	116,234	7,439	16.3
Nigeria	140,879,000	299,297	19,155	42.9
Japan	127,449,000	17,724	1,134	2.8
Mexico	105,330,000	15,326	981	2.9
Philippines	85,496,000	216,228	13,839	51.0
Vietnam	84,074,000	97,497	3412	12.8
Germany	82,409,000	3,339	100	0.4
Egypt	77,154,000	9,266	593	2.4
Ethiopia	74,661,000	124,710	7,981	33.7
Turkey	71,169,000	11,042	707	3.1
Iran	70,765,000	9278	594	2.6
Thailand	65,946,000	64,566	4,132	19.8
France	61,013,000	5,517	166	0.9
United Kingdom	60,261,000	4,189	118	0.6
Congo (DR)	59,077,000	125,538	8,034	42.9
Italy	58,645,000	2,807	84	0.5

Burden of Fungal Diseases

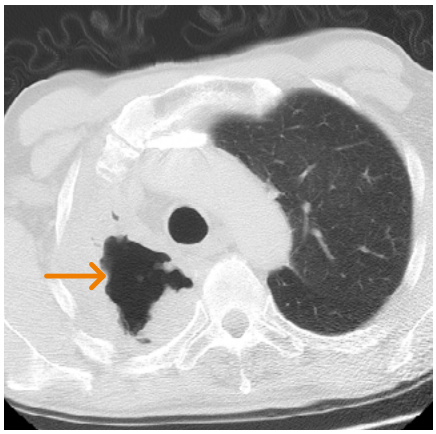
The radiological and clinical manifestations or CPA are similar to TB, although fever is uncommon. It is often mistaken for TB, especially smear negative TB. The key diagnostic test, the detection in serum of *Aspergillus* IgG is not widely available in LMICs. Approximately, 20 per cent of patients treated for TB will develop *Aspergillus* antibodies indicating infection and a large proportion of these patients develop CPA. The clinical symptoms and chest imaging signs are similar to TB. Misdiagnosis and mis-treatment is probably common. Alternative differential diagnoses for smear negative TB include the fungal infections histoplasmosis, coccidioidomycosis, paracoccidioidomycosis as well as non-tuberculous mycobacterial infection. Patients thought to have TB who fail to respond to therapy may be diagnosed with multi-drug resistant TB (MDR) and treated with second line agents. In 2012, the WHO estimated that there are ~4 million MDR TB cases with one million deaths (65); some of these patients probably have CPA. Treatment options for CPA are amphotericin B or itraconazole, or the newer azoles and echinocandins.

Fungal allergy and 'fungal asthma'

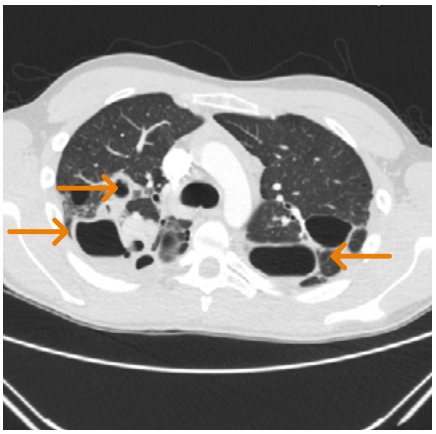
The number of people with asthma is about 300 million with adults affected comprising 197 million (4). Individuals with an atopic (allergic) tendency may develop fungal allergy of the lungs or sinuses. The air is full of fungal spores and hyphae. *Aspergillus* produces more fungal allergens than any other known organism. The entities in which fungal allergy of the lungs in asthmatics predominates include allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitization (SAFS) are collectively referred to as 'fungal asthma'. These patients have poorly controlled asthma requiring high dose inhaled corticosteroids and/or oral corticosteroids. Those with ABPA may cough up thick plugs or get obstructed airways, similar to pneumonia. Both may develop bronchiectasis as complications.

'We have no idea of the extent of most fungal diseases because the diagnostic capacity is not there, especially in countries north of Australia'

Professor Tania Sorrell



Above. Chronic pulmonary aspergillosis in the apex of the right lung after removal of the upper lobe for cancer. The walls of the cavity shows typical fungal growth on its surface.



Above. Severe bilateral chronic cavitary pulmonary aspergillosis in an 18 year old, after TB, who responded very well to voriconazole.

A patient with longstanding severe asthma comments

'I just can't breathe. It is so frightening - I start to panic. When do I call an ambulance? It happens so often, and often just before the sun comes up. Will it ever end?"

Burden of Fungal Diseases

There are six published estimates of ABPA prevalence (0.7-4.1%, median 2.5%) in asthma from South Africa, Ireland, Saudi Arabia, New Zealand, Iran and China. An estimate of 4.8 million adults with ABPA complicating asthma has been made (4). Rates for countries with populations over 50 million were also estimated (Table 3.3). All these rates could significantly underestimate the burden because on a limited time frame was studied, or overestimate rates because only the most severe cases are referred to a specialist. True population studies have not been done.

Assuming that 10% of the worst asthmatics are called severe, we know that a minimum of 33% of these patients are sensitized to various fungi, including *Aspergillus*. So a minimum number of 6.5 million adult asthmatics have SAFS (65). There is duplication between SAFS and ABPA depending on the severity of asthma and fungi to which the SAFS patients are reactive to. A small number of children also get ABPA and/or SAFS. Globally 489,000 are thought to die of asthma (20), and it is likely that a significant proportion of these patients have SAFS, possibly 50%. Cystic fibrosis patients also suffer from ABPA, as well as *Aspergillus* bronchitis (6), estimated at ~19,000 adults globally.

Table 3.3 Prevalence of adults with asthma and different estimates of ABPA depending on different prevalence estimates in patients referred to a specialist (4).

Country	Population (2005)	Adults with asthma	ABPA burden (lower) (0.7%)	ABPA burden (midpoint) (2.5%)	ABPA burden (upper) (3.5%)
Global total	6,512,276,000	193,477,000	1,354,000	4,837,000	6,771,689
China	1,312,253,000	19,645,469	138,000	491,000	688,000
India	1,130,618,000	20,331,609	142,000	508,000	712,000
United States	302,741,000	24,561,292	172,000	614,000	860,000
Indonesia	219,210,000	1,569,627	11,000	39,000	55,000
Brazil	186,075,000	13,968,105	98,000	349,000	489,000
Pakistan	165,816,000	3,788,659	27,000	94,000	133,000
Bangladesh	153,122,000	3,416,715	24,000	85,000	120,000
Russia	143,470,000	2,478,833	26,000	62,000	87,000
Nigeria	140,879,000	3,745,966	17,000	94,000	131,000
Japan	127,449,000	7,091,327	50,000	177,000	248,000
Mexico	105,330,000	2,194,915	15,000	55,000	77,000
Philippines	85,496,000	2,988,537	21,000	75,000	105,000
Vietnam	84,074,000	1,125,569	7,900	28,000	39,000
Germany	82,409,000	4,627,779	32,000	116,000	162,000
Egypt	77,154,000	2,496,526	17,000	62,000	87,000
Ethiopia	74,661,000	1,085,787	7,600	27,000	38,000
Turkey	71,169,000	3,424,403	24,000	86,000	120,000
Iran	70,765,000	2,469,321	17,000	62,000	86,000
Thailand	65,946,000	3,099,283	22,000	77,000	108,000
France	61,013,000	3,223,998	23,000	81,000	113,000
United Kingdom	60,261,000	7,138,150	50,000	178,000	250,000
Congo (DR)	59,077,000	2,021,738	14,000	51,000	71,000
Italy	58,645,000	2,193,394	15,000	55,000	77,000

Burden of Fungal Diseases

3D. Fungal keratitis

Fungal infection of the eye (keratitis) is thought to affect over 1 million adults and children globally. Infectious keratitis is common, and in temperate climates is usually bacterial (or viral) (>90%) but in tropical and semi-tropical areas is ~50% fungal. Risk factors related to injury to the eye from plant materials, contact lens, and possibly local healer products containing fungi. Early antifungal therapy saves sight, but late diagnosis or inadequate therapy results in loss of vision and sometimes the eye. In Tanzania, 8% of eyes had to be enucleated following fungal keratitis (67). If the eye can be saved, but the cornea is opacified, a corneal transplant can restore sight, if the cornea is not too badly damaged.

The most affected by fungal keratitis are young male agricultural workers (68), as well as children (Figure 3.12), and the impact on their lives is considerable.

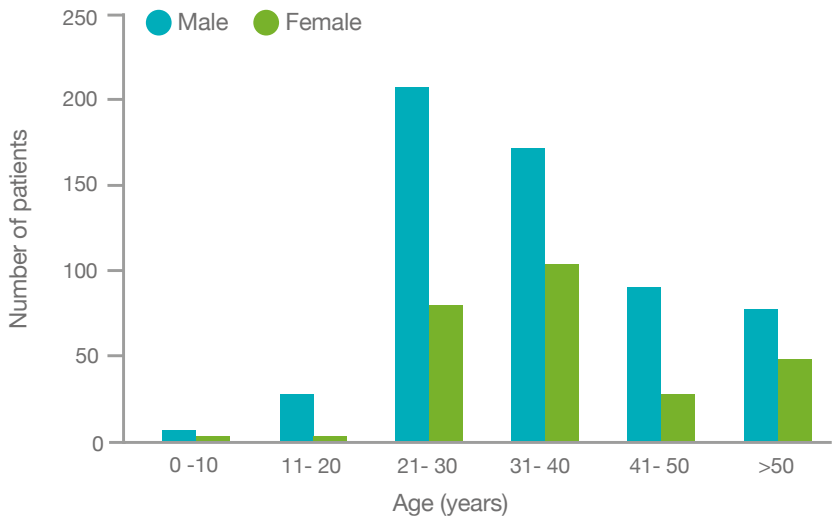


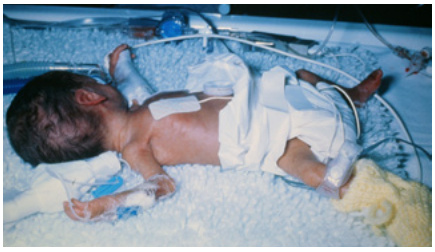
Figure 3.12 Age and sex distribution of fungal keratitis in India in a recent study (68). Note that 4% are children, and males are more frequently affected.

3E. Fungal infections in children

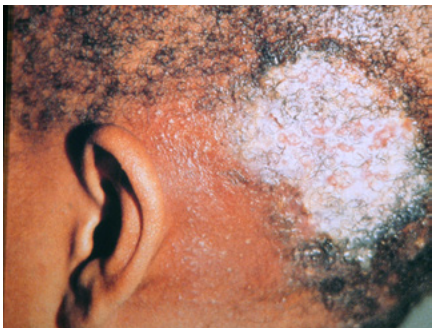
The largest burden of fungal infection in children is cutaneous, especially tinea capitis and ringworm (7). Probably half the billion people with fungal skin infection affected are children (69). Tinea capitis can be inflamed (kerion) leading to pain, discharge, secondary bacterial infection and scarring with permanent hair loss (70). Of the estimated 200 million children with tinea capitis, most are in our poorest communities. Shaving of the head is one solution, often adopted.

Premature birth and neonatal intensive care carry a substantial risk of invasive candidiasis, up to 10%, often hospital acquired through umbilical catheters. Children with untreated HIV infection present with PCP, usually around their first birthday, or in endemic areas with histoplasmosis. Cryptococcal infection in children is rare, about 2% of the global total.

As with adults, invasive aspergillosis, candidaemia, and PCP affect immunocompromised children, though at a slightly lower frequency than adults. Investigation in children for pulmonary fungal disease is more challenging than adults, because bronchoscopy and CT scanning are more difficult.



Above. An extremely low birthweight premature boy critically ill with *Candida* bloodstream infection.



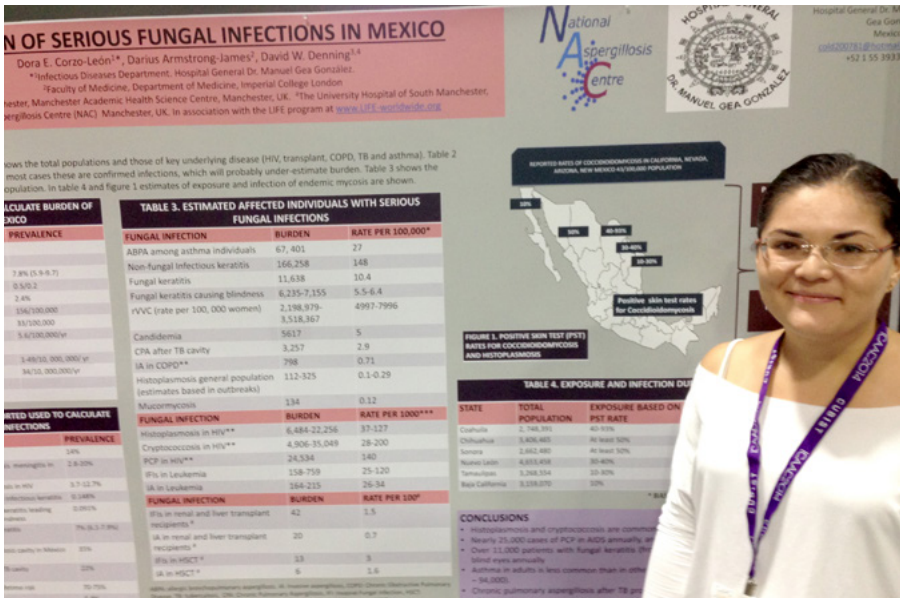
Above. A typical example of severe tinea capitis in a child from Africa.

Burden of Fungal Diseases

3F. Burden of serious fungal infections by country

Individual country estimates for the most populous countries have been made for chronic pulmonary aspergillosis after TB (2), CPA complicating sarcoidosis (5) and also allergic bronchopulmonary aspergillosis in adults with asthma (4) and in cystic fibrosis (6). Whole country estimates have been made for Argentina (71), Australia (71), Austria (72), Belgium (71), Brazil (70), Canada (74), Chile (74), China (73), Czech Republic (75), Denmark (78), Dominican Republic (77), Ecuador (71), Egypt (74), France (78), Germany (79), Guatemala (80), Hungary (81), India (73,82,83), Indonesia (74), Iran (84), Iraq (85), Ireland (85), Israel (87), Jamaica (88), Jordan (74), Kenya (89), Mexico (71), Mongolia (84), Nepal (90), Netherlands (73), New Zealand (74), Nigeria (91), Russia (92), Saudi Arabia (71), Senegal (93), Singapore (73), South Korea (84), Spain (46), Sri Lanka (94), Tanzania (95), Thailand (74), Trinidad and Tobago (84), Uganda (96), the UK (85), Ukraine (97), Vietnam (98) and Zambia (84). Others are ongoing.

GAFFI and **LIFE** have worked with local experts to estimate the burden of serious fungal infections in 47 countries. The variation between countries in the predicted and documented frequency of different fungal diseases is remarkable, and local epidemiology studies to confirm these major variations are warranted.



Above. Dr Dora Corzo-León from Mexico City presenting her poster on the burden of fungal infections in Mexico in 2014 at ICAAC.

Above. Dr Ali Osmanov presenting the burden of serious fungal infections in Ukraine at ECCMID 2014.

Above. Prof David Denning presenting the burden of fungal infections in the Dominican Republic at TIMM in 2013.