Global incidence and mortality of severe fungal disease

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Current estimates of fungal disease incidence and mortality are imprecise. Population at risk denominators were used to estimate annual incidence for 2019–21. Extensive literature searches from 2010 to 2023 were combined with over 85 papers on individual country and global disease burden. Crude and attributable mortality were estimated using a combination of untreated mortality, the proportion of patients who are treated, and percentage survival in treated patients. Awareness, guidelines, and accessibility of diagnostics and therapies informed the ratio of treated to untreated cases. Estimates do not include influenza or COVID-19 outbreaks. Data from more than 120 countries were included. Annually, over 2 113 000 people develop invasive aspergillosis in the context of chronic obstructive pulmonary disease, intensive care, lung cancer, or haematological malignancy, with a crude annual mortality of 1 801 000 (85·2%). The annual incidence of chronic pulmonary aspergillosis is 1 837 272, with 340 000 (18·5%) deaths. About 1 565 000 people have a *Candida* bloodstream infection or invasive candidiasis each year, with 995 000 deaths (63·6%). Pneumocystis pneumonia affects 505 000 people, with 214 000 deaths (42·4%). Cryptococcal meningitis affects 194 000 people, with 147 000 deaths (75·8%). Other major life-threatening fungal infections affect about 300 000 people, causing 161 000 deaths (53·7%). Fungal asthma affects approximately 11·5 million people and might contribute to 46 000 asthma deaths annually. These updated estimates suggest an annual incidence of 6·5 million invasive fungal infections and 3·8 million deaths, of which about 2·5 million (68%; range 35–90) were directly attributable.

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Introduction

Individual estimates of incidence and mortality for fungal infections have been accumulating over the last decade as more epidemiological data have been published. Despite the publication of burdens of serious fungal diseases for over 80 individual countries,[1] the totality of the disease burden remains elusive. Substantial data gaps persist, partly because surveillance is implemented in very few countries and for very few fungal diseases. The clinical impact of fungal diseases varies as fungi cause both life-threatening and sight-threatening infections, as well as substantial morbidity, in the case of long-term fungal diseases.

Reasonable estimates of specific fungal diseases are valuable for public health planning, diagnostic implementation, access to and development of antifungals, as well as appropriate responses to the growing problem of antifungal resistance. No vaccines are licensed or in clinical study for any fungal disease. Thus, improvement of diagnostic practice and antifungal prescribing and stewardship are all necessary to minimise deaths from fungal diseases, reduce unnecessary antibacterial and antifungal usage, and address infections caused by resistant fungi.

The first attempt to estimate the incidence of any fungal disease was published in 2009 for AIDS-associated cryptococcal meningitis.[2] This study was followed by an estimate of the incidence and prevalence of chronic pulmonary aspergillosis (CPA) after pulmonary tuberculosis.[3] A rough estimate of caseload and deaths from several fungal infections[4] was then followed by studies on CPA complicating sarcoidosis[5] and allergic bronchopulmonary aspergillosis (ABPA) complicating asthma.[6] Two updated estimates of AIDS-associated cryptococcal meningitis were published in 2017 and 2022, showing a progressive fall in incidence.[7,8] Other global estimates published include aspergillosis complicating cystic fibrosis,[9] recurrent vulvovaginal candidiasis,[10] fungal keratitis and consequent unilateral blindness,[11] and invasive aspergillosis complicating chronic obstructive pulmonary disease (COPD).[12] In 2017, a summary of 43 published country burdens allowed global estimates of some fungal diseases to be made;[13] to date, over 85 papers on individual country burden of diseases have been published, covering over 90% of the global population.[1]

This Review summarises the current data on the incidence and mortality of life-threatening fungal

Key messages

- New estimates indicate that over 6·5 million people annually are affected by an invasive fungal infection and chronic pulmonary aspergillosis
- This Review presents, to my knowledge, the first evidence-based global estimates of the incidences of invasive aspergillosis in patients in intensive care (omitting epidemics of influenza or COVID-19) and with lung cancer; invasive candidiasis in patients without a positive blood culture; pneumocystis pneumonia in patients with and without HIV; cryptococcal disease in patients without HIV; and histoplasmosis in patients with AIDS and coccidioidomycosis
- Overall crude mortality (approximately 3·8 million) was estimated using ratios of diagnosed and treated patients versus untreated patients, based on probable case finding, together with real-life mortality of treated cases and inferred mortality of untreated cases
- Attributable mortality is probably approximately 68% of crude mortality
- The largest contribution to deaths in these estimates comes from undiagnosed and, therefore, untreated cases

	Risk population (thousands; range)	Risk population (point estimate)	Comments	References
COPD	212 336–552 301	552 301 000	Only hospitalised patients deemed at risk of invasive aspergillosis	Hammond et al (2020),[12] Momtazmanesh et al (2023)[14]
Annual COPD hospitalisations	16 569–224 788	57 991 563*	GOLD stages 2–4 based on 30 countries	Hammond et al (2020)[12]
ICU beds	..	426 500	Conservative as includes only OECD countries plus China, India, Brazil, Argentina, South Africa, Colombia, and Ecuador	Appendix 1 p 4
Medical ICU bed admissions	..	20 758 400	Assumes 80% of ICU beds are medical and median stay duration is 6 days	Appendix 1 p 4
Leukaemia†	..	474 419	..	Global Cancer Observatory (2020)[15]
AML	86–197	118 629‡	Regional range is 18·2–41·6%	Dong et al (2020)[16]
Allogeneic HSCT	..	55 000	Uplifted from 38 425 in 2016	Neiderweiser (2022)[17]
Lung cancer	2207–2260	2 206 771	..	Global Cancer Observatory (2020),[18] Kocarnik et al (2022)[19]
Pulmonary tuberculosis	7607–8660	8093	645 340 in people with HIV	WHO (2021)[20]
Asthma	262 410–357 400	199 710 000 adults	5·4% of people aged 15–69 years	Song et al (2022),[21] Wang et al (2023)[22]

COPD=chronic obstructive pulmonary disease. GOLD=Global Initiative for Chronic Obstructive Lung Disease. OECD=Organization for Economic Cooperation and Development. ICU=intensive care unit. AML=acute myeloid leukaemia. HSCT=haematopoetic stell cell transplant. *10·5% of prevalence. †Including AML. ‡23·1% of annual incidence of all leukaemias.

Table 1: **Population at risk denominators used for estimating annual incidence or prevalence of fungal disease**

disease, with important transparent assumptions about the proportions of cases that are and are not diagnosed. For the first time, attributable mortality is also estimated, taking into account the fact that some patients with an invasive fungal infection have severe underlying disease, which might, in itself, ultimately be fatal.

See Online for appendix 2

Methods

Literature searches, conducted using PubMed and Google between July 15, 2023, and Aug 20, 2023, to include publications from Jan 1, 2013, until July 31, 2023, were combined with references listed in the retrieved full-text articles and major reviews of each topic (appendix 1 p 2). Searches focused on recent estimates of populations at risk (table 1); annual incidence of each fungal disease; observational studies of real-life outcomes (or if these data were absent, treatment trials); mortality; and, attributable mortality, using search terms such as "invasive aspergillosis AND mortality". Each published country burden article is a summary of all published and some unpublished data for that country up to the date of publication;[1] additional country searches were done to seek any new data published up to July 31, 2023.

See Online for appendix 3
See Online for appendix 1

Where possible, population at risk denominators were used to estimate annual incidence (table 1). Rather than attempt to recalculate these populations for a given year, the population estimates for the given period were used, usually 2019–21 but sometimes earlier; this approach resulted in a slight underestimation of burden in fast-growing populations, notably some African countries. The specific populations used for each estimate are listed by fungal disease (appendix 1 pp 3–26). A potential weakness of this estimation approach is the accuracy of the underlying disease prevalence or incidence data, which are also estimates. Incidence of candidaemia and pneumocystis pneumonia were taken directly from published work and, for candidaemia, adjusted upwards for missing country data, on the basis of the 2021 population[23] (appendix 2).

Annual incidence was based on deterministic modelling for most fungal diseases, using published incidence data for the relevant patient group, with a range if available or appropriate. In some cases, actual estimates were determined from available literature.

Mortality was estimated as a combination of untreated mortality, the proportion of patients who were treated, and percentage survival in treated patients (appendix 1 pp 3–26; appendix 3). There is moderate confidence in the outcomes of treated patients from multiple observational studies (and some prospective treatment trials, which can sometimes exaggerate benefit when implemented more broadly). There is less confidence in the natural course of undiagnosed and untreated patients. The ratio of treated to untreated cases is based on the following: general fungal disease awareness; underlying disease complexity; distinctiveness of the clinical or radiological presentation of fungal disease; sensitivity, performance, and availability of diagnostic tests; availability of antifungal drugs; quality of antifungal treatment (ie, itraconazole formulation bioavailability); and treatment affordability (when not provided to a population by national health-care coverage). National and international guidelines that are comprehensively collated[24] and antifungal stewardship programmes might influence all these factors. For example, as almost no *Histoplasma* antigen tests are available or done in Africa or southeast Asia,[25,26] disseminated histoplasmosis in AIDS is routinely misdiagnosed as tuberculosis or sepsis in these localities. In addition, most countries do blood cultures for suspected infection and when *Candida* spp

are grown, multiple guidelines and antifungal drugs are available for treatment and usually used. It is generally unknowable how many cases are missed and untreated because, had the diagnosis been made, treatment would have been administered in almost all cases, if available. The proportions of patients with each fungal disease who are treated have, therefore, been based on the author's deep knowledge of the diseases in question and a decade of engagement with practitioners from across the world. These mortality estimates are acknowledged to be an uncertain summation of multicountry data, with low confidence.

Overall (crude) mortality using published data was estimated, followed by attributable mortality. If there were no published data detailing attributable mortality, an informed estimate was made (appendix 1 pp 3–26; appendix 3) on the basis of the usual severity of the underlying disease or diseases, as well as the frequency of comorbid problems and their probable cumulative impact on survival.

Results

Overall, these estimates indicate that over 6·55 million people are affected each year by an immediately life-threatening fungal disease (figure 1), leading to over 3·75 million deaths (figure 2), of which about 2·55 million are directly attributable to that fungal disease (table 2). Additional data, commentary, and references are provided in appendix 1 (pp 1–26).

Four population groups were used to estimate the annual incidence of invasive aspergillosis. The percentage of patients with COPD admitted to hospital with invasive aspergillosis varies from 1·3% in Spain to 3·9% in China; a mean of 2·5% was applied, giving a probable total of 1513000 (range 753000–2273000).[12] More recent published data from China supports this estimate, with 5·3%[27] and 2·14%[28] of patients with COPD reported to have invasive aspergillosis. Invasive aspergillosis in patients with COPD is often not diagnosed, and there are no guidelines codifying diagnosis in this group; hence, the current ratio of diagnosed versus undiagnosed patients is 1:5. The overall mortality of diagnosed invasive aspergillosis complicating COPD varies from 43% to 72%,[12] and attributable mortality varies from 83% to 90%.[29,30] Thus, crude mortality is likely to be 1325000, of which 1060000 deaths are directly attributable to invasive aspergillosis, probably in part because of late diagnosis.

Invasive aspergillosis in patients admitted to general medical intensive care units (ICUs) varies from 1% to 5·0%.[31] In a prospective study of ventilator-associated pneumonia, which emerges in 5–40% of ICU patients on mechanical ventilation for 2 or more days, 12·5% had invasive aspergillosis.[32,33] A baseline estimate has been applied to avoid including years with severe influenza outbreaks and COVID-19 cases, which have a higher overall incidence of invasive aspergillosis. Higher incidence reflects proactive diagnostic approaches, and slightly different diagnostic criteria are used in different studies.[34] Here, a figure of 2·5% of patients admitted to medical ICUs having invasive aspergillosis was used, supported by a 25-year study from Spain, which found invasive aspergillosis in 2·8% of post-mortem

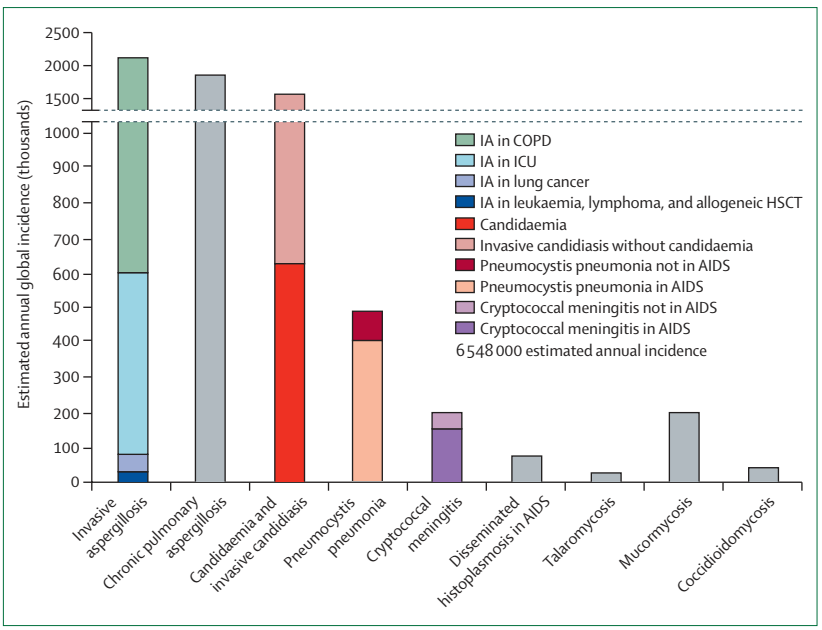

Figure 1: **Estimated annual incidence of life-threatening invasive mycoses, together with chronic pulmonary aspergillosis**

Omitted estimates include invasive aspergillosis in solid organ transplant and other less common immunodeficiency states, chronic pulmonary aspergillosis in many patients without pulmonary tuberculosis (depending on the accuracy of diagnosis), cryptococcosis not affecting the brain, all forms of histoplasmosis not in patients with HIV, primary coccidioidomycosis, fusarosis, paracoccidioidomycosis, sporotrichosis, mycetoma, chromoblastomycosis, and other rarer potentially lethal fungal infections. IA=invasive aspergillosis. COPD=chronic obstructive pulmonary disease. ICU=intensive care unit. HSCT=haematopoietic stem cell transplantation.

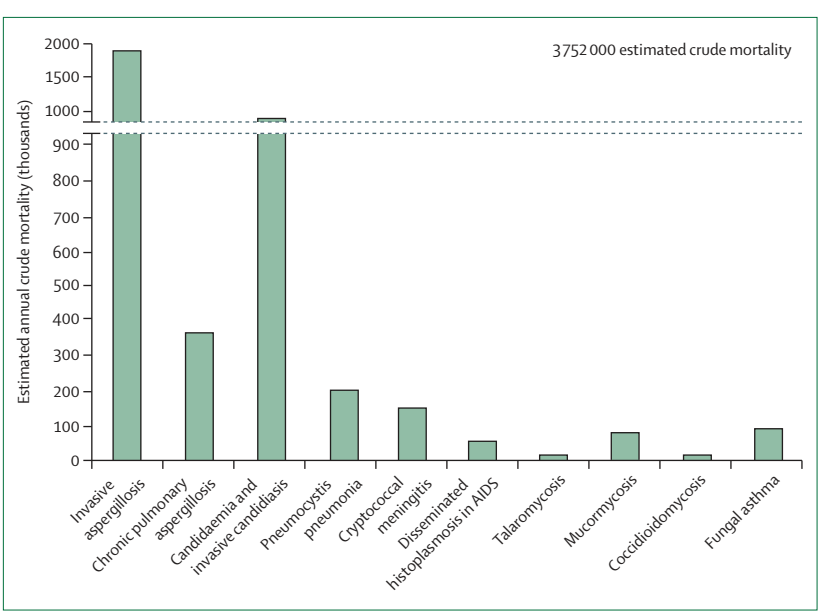

Figure 2: **Estimated crude mortality of severe fungal disease, worldwide**

	Mean annual incidence (thousands)	Treated mortality (%)	Untreated mortality* (%)	Ratio of treated to untreated cases*	Mean estimated deaths (thousands)	Percentage of deaths attributable to fungal infection (%)	Attributable deaths (thousands)
Invasive aspergillosis in COPD	1513 (753–2272)	43–72%	>95%	1:5	1325	~80%	1060
Invasive aspergillosis in ICU	519 (208–1038)	50% (46–82)	>95%	1:3	416	~50%	208
Invasive aspergillosis in leukaemia and lymphoma, and allogeneic HSCT	27	45% (30–57)	>95%	10:1	14	~80%	11
Invasive aspergillosis (lung cancer)	57*	51%	>95%	1:4	49*	~40%	19*
Chronic pulmonary aspergillosis	1837	8%	20%	1:12	340*	60% (0–85·7)	204*
Candida bloodstream infection	626	35% (8·7–77·3)	~90%	9:1	254	~65% (21–100)	165
Invasive candidiasis without positive blood culture	939	35% (27–60)	~90%	1:5	742*	~65% (21–100)	482*
Pneumocystis pneumonia in AIDS	400	15% (0–71)	>95%	4:1	140	90%	126
Pneumocystis pneumonia not in AIDS	105	40% (8–58)	100%	1:1	74	35% (30–90)	49*
Cryptococcal meningitis	194	60% (20–70)	100%	3:2	147	80% (63–68)	118
Disseminated histoplasmosis in AIDS	71 (47–95)*	30%	100%	1:10	66*	80%	53*
Talaromycosis	19	28%	>95%	3:1	9	90%	8
Mucormycosis	211	25%	100%	4:1	84	70%	59
Coccidioidomycosis (95% USA and Mexico)	30	..	..	10:1	2	90%	2
Fungal asthma	..	..	..	1:20†	92*	50%	46*
Totals	6548	NA	NA	NA	3752	NA	2548

Data are mean (range), unless stated otherwise. COPD=chronic obstructive pulmonary disease. ICU=intensive care unit. HSCT=haematopoetic stem cell transplant. NA=not applicable. *Low-confidence estimates requiring additional study. †Refers to antifungal treatment, not standard asthma therapy.

Table 2: **Global incidence and mortality of invasive fungal diseases**

examinations of ICU patients.[35] The annual incidence of invasive aspergillosis in ICU patients, not including epidemics of influenza or COVID-19, is estimated at 518 960 cases (range 207 548–1 037 920 [1–5% of all medical ICU patients]). Autopsy studies found that a minority (27–40%) of patients are diagnosed antemortem.[36–38] Two multicentre prospective studies in Italy and India found 6·31 and 7·8 of 1000 admissions, respectively, to have invasive aspergillosis.[39,40] Applying a figure of 7 of 1000 admissions, and assuming 33% are diagnosed, an alternative estimate is 435 918 cases. The crude mortality of diagnosed invasive aspergillosis in ICU patients varies from 46% to 82%, and attributable mortality is approximately 51%[41,42] (appendix 1 pp 4–5). Therefore, there are likely to be 416 000 deaths in patients admitted to ICU with invasive aspergillosis, of which about 208 000 are directly attributable to invasive aspergillosis (possible duplication with COPD cases is discussed in appendix 1 p 4).

Historically, invasive aspergillosis has been the most common infectious cause of death in patients with leukaemia, but the incidence has decreased in recent years because of antifungal prophylaxis and proactive diagnostic approaches. Patients fall into multiple risk categories, with acute myeloid leukaemia (AML) the primary risk group. On the basis of published surveys from France, Austria, and Taiwan (appendix 1 p 6), patients with AML have been assumed to comprise 50% of all invasive aspergillosis cases in patients with haematological malignancy or lymphoma. In addition, 10% of patients with AML (n=118 629) are assumed to develop invasive aspergillosis (this percentage is higher without antifungal prophylaxis and lower with prophylaxis), giving an incidence of 23 726 globally (table 2). This figure excludes patients undergoing haematopoetic stem cell transplants, which increases the estimate by about 3300 patients, taking into account about 55 000 allogeneic stem cell transplant procedures globally[17] and assuming invasive aspergillosis will occur in 6% of these patients (range 2·2–8·2; appendix 1 p 6).[43] Most of these patients are on antifungal prophylaxis, but this prophylaxis is not always targeted against *Aspergillus*. There is very little duplication with invasive aspergillosis occurring during the initial treatment of leukaemia. Mortality from invasive aspergillosis in leukaemia varies from 30·3% to 56·5% in multiple case series (n=12 000; appendix 1 p 6–7), and an attributable mortality of 80% is assumed, to account for some unresponsive leukaemias and other complications leading to death (table 2). Invasive aspergillosis often delays cycles of chemotherapy, causing worse leukaemia outcomes, even if this fungal disease is subsequently not the direct cause of death.[44]

Two estimates indicate that about 2·2 million cases of lung cancer occur annually (table 1). An estimated 2·6% of patients with lung cancer develop invasive aspergillosis[45] (table 2). Testing for galactomannan in both serum and bronchoalveolar lavage in 290 of 2543 patients with lung cancer in Taiwan found 34 (11·7%) with invasive aspergillosis (1·3% of all cases).[46] Use of dexamethasone as an antiemetic for chemotherapy might be partly responsible. A study in Denmark found 1·6% of suspected

lung cancer cases to have aspergillosis (n=35 300, if extrapolated globally).[47] Apparently progressive lung cancer might be due to invasive aspergillosis.[48] Of the estimated 57 375 patients with invasive aspergillosis, only 25% are assumed to be diagnosed. Mortality of patients with invasive aspergillosis is 51%[45] (49 000 deaths), 40% of which is attributable to invasive aspergillosis (about 19 000 attributable deaths).

In summary, the best estimate for invasive aspergillosis incidence has risen from more than 200 000 cases annually[4] to 2 116 362 (27·2 per 100 000 population), primarily because of the addition of cases of COPD and lung cancer with a wide potential range (table 2). These figures do not specifically include recipients of solid organ transplant, patients with some solid tumours, other immunocompromised patients, or many liver failure patients, which altogether probably number fewer than 100 000 annually; many of these patients are treated in ICUs, which could introduce duplication. A crude mortality of 1 803 000 (85·2%) is anticipated, of which 72% is attributable to aspergillosis.

In this Review, the estimates of CPA incidence and mortality include only patients who have, or are thought to have, pulmonary tuberculosis, ignoring many patients with other underlying types of lung disease who develop CPA. A 2019 estimate of CPA related to pulmonary tuberculosis in India[49] (the country with the largest burden of tuberculosis globally) included cases that were misdiagnosed as pulmonary tuberculosis, co-infections of tuberculosis and CPA, cases occurring during the first year after tuberculosis diagnosis, and CPA arising 1–5 years after successful treatment of pulmonary tuberculosis. In this Review, WHO's global tuberculosis figures from 2020[19] were used for modelling, yielding 8 093 400 pulmonary tuberculosis cases, of which 645 340 are co-infected with HIV; overall, 41% are clinically diagnosed without laboratory confirmation. The CPA model finds an incidence of 1 390 766 for new CPA cases from newly presenting tuberculosis cases (with 153 029 deaths, 12·5% of overall tuberculosis deaths). In addition, 446 505 new CPA cases are estimated to have presented in 2020 in people who had pulmonary tuberculosis in the previous 5 years, an incidence of 1 837 272 new cases (23·6 per 100 000 population). This incidence estimate excludes a 5-year prevalence estimate (appendix 1 p 9). CPA mortality is about 20% (range 0–40) in the first year after presentation and 7·5% annually thereafter over 5 years, yielding a 5-year mortality of 50% (range 16·4–80).[49] Attributable mortality varies from 4·8% (in patients with fibrocystic sarcoidosis) to 85·7%; 60% has been used here (appendix 1 p 10). Detailed mortality data on pulmonary tuberculosis as the only underlying disease are absent. It is likely that about 340 000 patients with CPA die within the first year of developing the disease. Of these deaths, 204 000 are attributable to CPA (table 2). This figure is similar to the 2011 estimate of 372 385 annual deaths from post-tuberculosis CPA, which was based on global pulmonary tuberculosis data from 2007.[3]

The previous estimate of annual incidence of more than 400 000 for bloodstream *Candida* infections (candidaemia)[4] is replaced by an estimate of 626 081 (8·05 per 100 000 population). This new estimate is based on 98 individual country estimates (91·8% of the global population) in individual country burden papers or abstracts published from 2013 to 2023 (appendix 2).[1] Annual incidence rates vary by country, from 1·87 per 100 000 population in Australia to 21 per 100 000 and 21·8 per 100 000 in Pakistan and Italy, respectively; countries without data are assumed to have a rate of 5·0 cases per 100 000 population. Variations within country can be large, as shown by a study in Belgium that found candidaemia incidence rates differing by up to 20-fold among 30 hospitals (from 0·07 to 1.43 per 1000 hospital admissions), without any obvious explanation.[50] The published mortality of candidaemia in 32 studies in adults and 17 studies in children and premature infants varied from 8·7% in children in all settings in China to 77·3% in adults in ICUs in Brazil (appendix 1 pp 11–12). Here, treated mortality of 35% and untreated mortality of 90% were used, leading to a total mortality of 254 000. Attributable mortality in 16 studies also varied substantially, from 21% to 100% (appendix 1 p 14); 65% has been used here, yielding 165 000 attributable deaths.

The incidence of invasive candidiasis without a positive blood culture, including intra-abdominal (or peritoneal) candidiasis, has also been estimated. Blood culture is approximately 40% sensitive for invasive candidiasis, compared with non-culture methods and autopsy[51] (appendix 1 p 15). Increased amounts of blood drawn and cultured increase yield; low blood volumes cultured, antifungal prophylaxis, and empirical therapy reduce yield (appendix 1 p 15). The annual incidence of invasive candidiasis with a negative blood culture is therefore 150% higher than that of candidaemia, at 939 121 cases (12·1 per 100 000 population). Unlike in candidaemia, where it is assumed that 90% of cases are diagnosed and treated, only 20% of cases of invasive candidiasis with a negative blood culture are assumed to be treated. The estimates for crude and attributable mortality for this group are less well supported by the literature, primarily because there is no gold standard (other than a complete autopsy) for diagnosis; thus, the percentages used for candidaemia have also been used for invasive candidiasis. Therefore, it is likely that 742 000 people die annually with invasive candidiasis, and 482 000 of these deaths are attributable to invasive candidiasis. Improved diagnosis is required to validate these figures.

The previous estimate of over 400 000 cases of pneumocystis pneumonia[4,13] is supported by the new estimate in this Review, with about 400 000 cases estimated in people with AIDS and 105 000 in other immunocompromised patients (6·5 cases per 100 000 population). These revised estimates are based on published country

	Cryptococcal meningitis incidence in AIDS*	Immunodeficiency unrelated to HIV	No underlying disease	New regional estimates
Africa (excluding north Africa)	82 000	4100 (5%)	10 250 (13%)	96 350
Asia and Pacific	44 000	11 000 (25%)	6600 (15%)	61 600
Latin America and Caribbean	13 700	1713 (13%)	1370 (10%)	15 070
Eastern Europe and central Asia	10 000	3000 (30%)	2500 (25%)	15 500
Western Europe and North America	2000	800 (40%)	500 (25%)	3300
Middle East and north Africa	400	80 (20%)	60 (15%)	540
Totals	152 000	26 693	21 280	193 973

Data are n or n (%); for data that are n (%), n=cryptococcal meningitis incidence in AIDS. *AIDS-related incidence from Rajasingham and colleagues.[8]

Table 3: **Estimates of annual incidence of cryptococcal meningitis in different populations, by region**

data (appendix 1 p 17; appendix 2), with rates varying hugely by country depending on HIV prevalence and the proportion of patients whose HIV infection is uncontrolled by antiretroviral therapy (ART). Annual incidence of pneumocystis pneumonia in individual countries varies from 0·1 per 100 000 population (Bangladesh, Hungary, Jordan, and Oman) to as high as 40 per 100 000 (Cameroon), 51·6 per 100 000 (Kenya), 48·2 (Nigeria in 2014, before the revision of the total HIV prevalence), 61·8 per 100 000 (Malawi), and 151 per 100 000 (Mozambique; appendix 1 p 17; appendix 2). In 84 countries with a published annual incidence, the number of cases was 376 638. This figure has been conservatively increased to 400 000 to account for missing countries. In high-income nations, mortality for pneumocystis pneumonia in AIDS ranges from 0% to 15%, whereas a systematic review of sub-Saharan African countries found an overall mortality of 18·8% (range 0–71).[52] In this Review, a crude mortality rate of 15% was used and 90% of deaths were assumed to be attributable, yielding 140 000 deaths and 126 000 deaths, respectively.

To estimate pneumocystis pneumonia in patients without AIDS, the incidence in multiple Organization for Economic Cooperation and Development (OECD) countries varied from about 0·8 to 3 cases per 100 000, so an incidence of 2 per 100 000 population in 36 OECD countries was used (appendix 2)—ie, a total of 26 400. Populous country estimates have been added to this total; namely, for India (32 691 cases; 2·35 per 100 000), Indonesia (15 400 cases; 5·75 per 100 000), and China (9241 cases; 0·64 per 100 000),[1] giving an overall total of 83 732 cases. Adding an arbitrary 25% to account for remaining countries not yet estimated produces an annual incidence of 104 665 (table 2). Crude mortality for treated cases of pneumocystis pneumonia in patients without AIDS is about 40% (range 8–58; appendix 1 p 18), and mortality in untreated cases is estimated at 100%. 50% of diagnoses are assumed to be missed, resulting in an estimated 74 000 deaths from pneumocystis pneumonia in patients without AIDS. Assuming 35% (range 30–100) of deaths are directly attributable to pneumocystis pneumonia (appendix 1 p 18), 49 000 deaths are estimated to be directly caused by this disease.

Cryptococcal meningitis incidence in AIDS has been falling with the roll-out of ART for HIV infection, down from 223 100, based on 2014 HIV data, to 152 000, based on additional incidence data and HIV-related data from 2019 to 2020.[7,8] The first estimate of non-AIDS-related cryptococcal meningitis has been added to these figures, adding approximately 41 000 cases—about half occurring in non-immunocompromised people. This estimate derives from 22 publications from 20 countries, where the relative percentage of cases of cryptococcal meningitis in patients with AIDS contrasts with those in apparently healthy and immunocompromised people (appendix 1 pp 19–20). The regional estimates of Rajasingham and colleagues[8] were used to compute new regional estimates (table 3).

Mortality in cryptococcal meningitis varies widely, depending on how early the diagnosis is made and whether amphotericin B, flucytosine, or fluconazole, or a combination thereof, is used for treatment. Other key factors affecting survival include control of raised intracranial pressure, the timing of starting ART, and treatment adherence. Rajasingham and colleagues estimated 112 000 cryptococcal-related deaths (sensitivity analysis 79 000–134 000), accounting for approximately 19% of AIDS-related mortality.[8] Thus, a crude mortality of 60% (range 20–70) was used for treated cases of cryptococcal meningitis, and 100% for untreated cases; it was assumed that 60% of cases are diagnosed. These figures lead to an annual global mortality of 147 000 for all cases. Attributable mortality is close to 100% in patients with AIDS and 62·7–68·3% patients without AIDS; thus, using a figure of 80%, 118 000 deaths are directly attributable to cryptococcal meningitis (table 2). These estimates exclude cryptococcal antigenaemia, pneumonia, and other cryptococcal infections not affecting the brain.

The estimate of 71 450 cases annually (appendix 1 p 21; table 2) for disseminated histoplasmosis in AIDS is uncertain, primarily because of a scarcity of data from Africa and southeast Asia. Conventional diagnosis with microscopy and culture is slow and very insensitive—only antigen or PCR testing reveals the true extent of this infection. This estimate ignores (because of a lack of data) acute and subacute disseminated histoplasmosis in people without AIDS and cases of chronic pulmonary histoplasmosis. Although untreated disseminated histoplasmosis is almost certainly fatal, response to therapy yields survival of about 70%.[53,54] Given the lack of antigen diagnostics, it is assumed that only 10% of cases of disseminated histoplasmosis in AIDS are currently diagnosed worldwide. No estimates of attributable mortality have been published, but because a minority of these patients have co-infections, some with tuberculosis,

a provisional figure of 80% was used. Overall, therefore, 66 000 deaths are estimated in patients with disseminated histoplasmosis (approximately 10% of all HIV-related deaths), of which 53 000 are attributable to this disease.

Talaromycosis is especially prevalent in AIDS and is localised to southeast Asia, apart from a few cases occurring in travellers from this region. A systematic review summarised publications up to 2019 and found country prevalence of talaromycosis in HIV-infected patients to be 6·4% in Viet Nam, 3·9% in Thailand, 3·3% in southern China, 3·2% in northeastern India, and 2·1% in Malaysia, with no data for Laos, Cambodia, Myanmar, Singapore, Indonesia, Philippines, Papua New Guinea, or Bangladesh;[55] however, the available denominators are unreliable. Here, a published abstract estimate of 17 300 annual cases was used for estimation[56,57] and increased by 10% to account for non-HIV-infected patients—a total of 19 030. Narayanasamy and colleagues found talaromycosis mortality to vary from 6·5% to 33·3% in different countries;[57] here, a mortality of 28% was used for treated cases and greater than 95% for untreated cases (table 2). As there are no data on attributable mortality, a figure of 80% was used, yielding an anticipated 9000 annual deaths, with 8000 attributable to talaromycosis.

The previous estimate for mucormycosis in 2012 was too low, at more than 10 000 cases, but data were lacking.[2] With new data, primarily from India, an incidence of 211 000 (2·7 per 100 000) is estimated (the outbreak of mucormycosis in COVID-19 is not accounted for in this estimate). This estimate anticipates an annual incidence of 2 cases per million (n=13 000) in all countries except India and Sri Lanka, where mucormycosis incidence is estimated at 14 cases per 100 000[58] population (appendix 1 p 23; table 2). The global hotspot for mucormycosis is India and the rare, but distinctive, renal mucormycosis appears to be exclusive to that country. A recently completed systematic review of 10 335 published cases and case series of mucormycosis (which includes many cases arising during the COVID-19 pandemic) found 25·7% mortality in treated patients and 100% in untreated patients.[59] Although most cases of mucormycosis are clinically obvious, some are not; thus, here, it was assumed that 80% of cases are recognised and treated. The few available figures for attributable mortality vary between 33·3% and 58%. In this Review, a figure of 70% was used, to account for the lack of appropriate expertise and unaffordability of treatment in many countries. These figures yield a crude global annual mortality of 84 000, of which 59 000 deaths are attributable to mucormycosis (table 2).

This Review provides, to my knowledge, the first estimate of the incidence of severe forms of coccidioidomycosis in the Americas. This estimate is based on the 2019 US surveillance report[60] combined with a published estimate from Mexico,[61] giving a total annual incidence of 30 043, including a 5% contribution from other countries (table 2). This estimate ignores asymptomatic exposure and self-resolving valley fever. If 90% of cases are diagnosed and treated and attributable mortality is 90%, about 2042 annual deaths related to coccidioidomycosis are probable, but this estimate needs additional support from epidemiological data (appendix 1 p 24).

The global burden of asthma is substantial, and many additional data have emerged in the last decade linking severe asthma to fungal allergy (sensitisation).[62] Using an asthma prevalence of 199·7 million people aged 15–69 years,[21] 10% of such cases were assumed to have severe or poorly controlled asthma after optimising inhaler therapy. If 40% of these adults are sensitised to fungi (appendix 1 pp 25–26), an estimated 8 million have severe asthma with fungal sensitisation. An estimate for ABPA cases was added to this figure, assuming 2·5% of all adults with asthma seen in secondary or tertiary care have ABPA; this proportion was used for all countries except India, where 5% was used (appendix 1 pp 25–26). Children with ABPA and allergic bronchopulmonary mycosis have been omitted as prevalence estimates are scarce (appendix 1 p 26), and there is probably duplication (based on overlapping diagnostic criteria) with severe asthma with fungal sensitisation. A prevalence of 11 690 000 adults with fungal asthma is probable (150 per 100 000 population; table 1).

The global annual mortality from asthma is estimated at 461 069.[14] Given the general uncertainty about the contribution of fungal sensitisation and airway infections to deaths from asthma, a conservative assumption of 20% of asthma deaths directly linked to fungal allergy was used. Therefore, it is probable that there are 92 214 fungal allergy-linked asthma deaths annually (table 2). Of these deaths, perhaps only 50% (n=46 000) are directly attributable to fungal diseases and addressable with antifungal or other directed therapies, given the many comorbidities of most of these older patients who die of asthma. Most cases of fungal asthma are not currently diagnosed (table 2).

Discussion

It is likely that over 6·55 million people globally have a life-threatening fungal infection each year. These new estimates show major shifts in incidence from generally accepted figures used in the last decade.[4,13] The barriers to any such credible estimation are many and include the scarcity or inaccuracy of appropriate denominators for all patients at risk; scarcity of adequate epidemiological data from many countries for some fungal diseases; and, uncertainty (which remains) about the proportions of patients diagnosed with a given infection, compared with the total number of cases. Other challenges to any estimation include imprecision of diagnosis (and variable internationally agreed diagnostic criteria), especially if multimodal, as in invasive and chronic aspergillosis and

invasive candidiasis without a positive blood culture. Nonetheless, global and national estimates of lethal and highly morbid fungal diseases are critical to health system capacity building, especially if a problem is frequent and a substantial cause of death or severe morbidity. These new estimates are necessarily crude, with large variability in the underlying risk populations, major regional differences, considerable differences in the proportions affected in different studies, and uncertainty in the mortality rate of undiagnosed and untreated patients and in the ratio of diagnosed to undiagnosed patients for a given disease.

Some fungal infections are globally important, with modest regional variations, whereas others are regional in occurrence. Regionally variability has been considered for each estimate in which it was known to be numerically important. A particularly challenging estimate was cryptococcal meningitis in non-HIV patients, which is global in occurrence but with major regional variations. In this case, regional estimates for AIDS-associated cryptococcal meningitis[8] were used. Other fungal diseases partly or fully estimated regionally are mucormycosis and ABPA (both more common in India), coccidioidomycosis (primarily in the USA and Mexico), pneumocystis pneumonia, cryptococcal meningitis (more common in people with AIDS and in Africa), and talaromycosis (southeast Asia). Omitted from consideration were some less common, regionally important fungal infections, which are much less frequent and linked mostly to morbidity rather than deaths, including blastomycosis, chronic pulmonary histoplasmosis, paracoccidioidomycosis, mycetoma, and fungal keratitis.

This Review presents new estimates of 3 752 000 for overall annual deaths and 2 548 000 for attributable annual deaths from fungal disease. Globally, there are about 55·4 million deaths annually.[63] Ischaemic heart disease is estimated to be responsible for 16% of the world's total deaths, followed by stroke and COPD, which are responsible for about 11% and 6% of total deaths, respectively. Our estimate assumes about a third of the 3 227 873 COPD deaths are attributable to invasive aspergillosis, which needs validation with more studies of better quality, given the general difficulty in diagnosing aspergillosis and absence of consensus diagnostic guidelines for this entity. Lower respiratory tract infection (not including tuberculosis) comprises the world's most deadly communicable disease syndrome and is ranked as the fourth leading cause of death, with 2·6 million lives lost in 2019;[63,64] some of these deaths are attributable to aspergillosis and pneumocystis pneumonia. Pulmonary tuberculosis was classified as the cause of death in 1 208 044 people in 2019;[20] this estimate suggests that many of the 340 000 CPA deaths could be misattributed to pulmonary tuberculosis. CPA deaths are likely to be underestimated in the Review, as only incident cases of CPA were considered, rather than prevalent ones. However, direct data on CPA deaths in younger patients with pulmonary tuberculosis-like presentation are missing—CPA mortality data are derived from older patients with other pulmonary underlying diseases in high-income countries.[49] Of the estimated 311 594 leukaemia deaths globally in 2020,[16] 14 000 (4·5%) could be attributable to invasive aspergillosis and some (unquantified) to other fungal infections, especially in AML. Lung and bronchus cancer deaths stand at 1·8 million,[18,19] with our estimate indicating that aspergillosis is implicated in 49 000 deaths (2·7%). Cases of invasive aspergillosis in solid organ transplants were also omitted to minimise duplication with the estimation of invasive aspergillosis in ICU patients. Most of these transplants are renal, with over 95 000 done in 2021. However, invasive aspergillosis is uncommon in renal transplant recipients, with attack rates of 0·4–2·3%.[65]

Both severe influenza and COVID-19 have led to a substantial increase in the incidence of invasive pulmonary aspergillosis[66] and, in the case of COVID-19, *Candida* bloodstream infection[67] and mucormycosis.[68] In this Review, the approximate incidence of invasive aspergillosis in ICU patients has been estimated, which includes patients with multiple underlying diseases. However, given the number of years over which underlying disease information has been collected, these estimates are also likely to include many cases of severe endemic influenza. To avoid inflating burden estimates here, the many papers documenting COVID-19-associated fungal infections specifically have not been used in the present estimation.

It is conventional to add confidence intervals or sensitivity analyses to estimates of this sort. Variation in the literature has been indicated in table 2 and detailed in appendices. Some wide variations were seen, and calculations using these data would imply global extrapolation from a single-centre, regional, or national study, which would be likely to introduce different errors or biases. As more data are generated (which is both hoped for and expected), tighter and more precise estimates with meaningful confidence intervals will become possible. Individual country estimates can be computed using the spreadsheet in appendix 3.

The largest potential errors in the mortality estimates are likely to be introduced by selecting precise figures for untreated mortality (all >90% except CPA, which is 20%), combined with the ratio of treated to untreated cases. Both these estimates are unknowable with current data and might remain so for years to come. The natural course of undiagnosed and untreated patients is only possible to ascertain with a natural experiment, using high performance diagnostics, but such a study would be impossible for ethical reasons, as those units able to diagnose will almost always treat. Only during the COVID-19 pandemic was it possible to ascertain this information for mucormycosis,[57] because India had a

shortage of amphotericin B, and mucormycosis diagnosis relies on conventional diagnostics. In this Review, the ratio of treated to untreated cases was based on the distinctiveness of the clinical or radiological presentation, the sensitivity and availability of diagnostic tests, general disease awareness among health-care professionals, antifungal drug availability, quality (ie, itraconazole formulation bioavailability) and affordability (when not provided to a population) of antifungal treatment, and underlying disease complexity, together with national and international guidelines[23] and antifungal stewardship programmes. Inevitably, there is huge variation in these ratios by hospital, region, and country. However, to omit all undiagnosed cases because of uncertainty would introduce even larger errors in mortality for most fungal diseases.

Determining attributable mortality is also far from precise, especially in patients at risk of fungal disease. Clinicians face considerable challenges when determining the cause of death. For example, if a patient with AIDS and a very low CD4 count has both disseminated histoplasmosis and pulmonary tuberculosis and subsequently dies, the clinician must decide whether the death is attributable to tuberculosis, histoplasmosis, or AIDS. As another example, if an older person in intensive care with longstanding diabetes, clinically significant renal impairment, and pneumonia then develops a bloodstream *Candida* infection and dies, the clinician must decide whether the death is due to *Candida* infection or (more likely) with *Candida* infection. Such judgements are clinically difficult and vary by perspective. However, it is clear that not everyone with an invasive fungal infection always dies as a direct result of the infection. The published data support a range of attributable mortality percentages from 0% to 100% in individual studies and from 35% to 90% collectively—thus, overall, about 68%.

Given the major improvements in the performance, costs, and ease of use of diagnostics for fungal disease in the past decade,[69] as well as the inclusion of lower-priced antifungal agents on the WHO List of Essential Medicines,[70,71] it should be possible to make substantial progress in addressing the excess mortality of fungal disease, alongside minimising morbidity. WHO called for this course of action in their release of the Fungal Pathogen Priority List in 2022,[72] noting poor epidemiological data for fungal disease, in terms of positive fungal cultures with organism identification. In this Review, estimates focus on fungal diseases, regardless of whether a pathogen was or was not cultured.

An estimate of the prevalence of fungal asthma has been included, given asthma deaths in excess of 400 000 globally.[14] Many more data from multiple countries are required to estimate fungal asthma prevalence with confidence, but given the documented clinical value of antifungal therapy for these patients and its much lower costs compared with biologics, a conservative estimate of prevalence and mortality was presented to highlight the issue. Fungal asthma is a neglected topic of epidemiological study, given its prevalence, relative simplicity of diagnosis, and the opportunity for treatment with existing and generic antifungal agents.

In conclusion, the incidence of fungal disease is substantially more frequent than previously thought. Improved clinical awareness, appropriate sampling, and timely laboratory diagnostic testing, combined with imaging, could definitively reduce the substantial number of mostly avoidable premature deaths from life-threatening fungal disease.

Contributors

DWD conceived, researched, drafted, rewrote, and finalised all elements of this Review and takes full responsibility for all errors and omissions.

Declaration of interests

DWD and his family have held founder shares in F2G (a University of Manchester spinoff antifungal discovery company) since 1998 and share options in TFF Pharmaceuticals. DWD acts or has recently acted as a consultant to Pulmatrix, Pulmocide, Biosergen, TFF Pharmaceuticals, Pfizer, Omega, Novacyt, Rostra Therapeutics, MucPharm, Mundipharma, Lifemine, and Cipla. He chairs a data review committee for Pulmocide and was a phase 1 medical monitor for Biosergen. In the last 3 years, DWD has been paid for talks on behalf of BioRad, Basilea, and Pfizer. He is a longstanding member of the Infectious Disease Society of America Aspergillosis Guidelines group, the European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines group, and the One World Guideline for Aspergillosis.

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