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Supplementary appendix 1

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Supplement 1 – **Search strategy, data sources, assumptions and references**

Search strategy; Numerous literature searches from January 2013 to July 2023 using Pubmed (and for global incidence of underlying disease also Google) were done. The objective of the searches to establish the population at risk prevalence was to identify (the most) recent credible, global source for underlying disease. For TB and HIV/AIDS, WHO figures were used and for cancer Globocan. Other data sources are referenced below and varied substantially. Specifics are given in **purple text** against each section below.

To establish the relevant frequency/incidence is each patient population, the search term 'incidence' was combined with the relevant fungal condition (i.e. 'aspergillosis') from 2013 onwards in Pubmed all paper abstract that were relevant read and included in the supplementary material below. This was supplemented by searching on The Aspergillus Website (www.aspergillus.org.uk) and in my own extensive collection of articles, and in the reference lists of retrieved papers. Papers were excluded if the denominator was unclear, or the fungal disease numerator was merged with other infections (i.e. 'invasive mould infection, without differentiation), or the populations affected were mixed so that the individual underlying disease entities could not be evaluated separately. The objective of these searches was to establish the range and then select a middle value to make a point estimate. It is likely some papers and abstracts have been omitted, but only if these studies were very large and had quite different percentage attack rate estimates, would the point estimates vary substantially. Additional country searches were done for all countries for which there were candidaemia/invasive candidiasis or *Pneumocystis* data summarised in that country burden paper (Supplement 2) to check that no new data had been published since the searches had been done for that country. Of note stringency (or confidence) in the diagnosis of that particular conditions was not taken into account as longs as cases were deemed probable or confirmed using standard criteria; only studies with poor diagnostic technique (i.e. defining aspergillosis by culture alone) were excluded.

The next steps were to estimate mortality and attributable mortality. Pubmed searches using 'mortality' OR 'death' were combined with the fungal condition (as above) to identify the range of observations of survival. Longer term and larger observation studies searches were identified, from as many parts of the world as possible, and small case series or case reports excluded. All retrieved papers with clear numerators and denominators are listed below and then a judgement was made about which percentage to use, as justified below.

Underlying disease prevalence, fungal disease incidence, mortality and attributable mortality.

This supplement is arranged in the same sequence of fungal diseases as the paper, with each section set out as follows:

- Risk group denominator or sum of available data
- Annual incidence (point estimate highlighted in green, if that is the estimation approach)
- Crude (overall) mortality and attributable mortality (individual estimates highlighted in yellow)

COPD hospitalisations. Search (Pubmed and Google): "COPD prevalence" The prevalence of COPD varies by a factor of about 2, from the 2010 BOLD study of 384 million (GOLD, 2023 report) https://goldcopd.org/2023-gold-report-2/ , a recent Global Burden of Disease estimate from 2019 using different methodology of 212,335,981 (GBD, 2023) https://pubmed.ncbi.nlm.nih.gov/37229504/ to 552,300,599 (stages II-IV) (Hammond, 2020) https://pubmed.ncbi.nlm.nih.gov/32912168/ , with other estimates between these figures, including an older WHO estimate of about 300 million. Increasing smoking rates in developing countries presage a rise in prevalence (GOLD, 2023). The key denominator used for calculating invasive aspergillosis (IA) incidence in COPD was the number of COPD patients admitted to hospital at least once annually, which is variable by region and country from 3% in Japan to 40.7% in United Arab Emirates (Hammond, 2020). Only Hammond et al have extrapolated this figure globally (from data in 30 countries), based on data generated as part of the BREATHE study from Algeria of 10.5% annually, a total of 57,991,563.

Annual incidence of IA in COPD patients. Search: "COPD" AND "aspergillosis" The presumption is that only those with COPD exacerbations or severe COPD are admitted to hospital and the usual practice of corticosteroids, often with antibiotics, puts these patients at risk of IA. All the published studies assessing IA in these patients are based on hospital admissions. The percentage of COPD admissions with IA varies from 1.3% in Spain to 3.9% in China (Guinea, 2010; https://pubmed.ncbi.nlm.nih.gov/19906275/ ; Xu, 2012 https://pubmed.ncbi.nlm.nih.gov/22023558/ ; Hammond, 2020 https://pubmed.ncbi.nlm.nih.gov/32912168/), and a mean 2.5% was applied. More recent published data from China of IA in COPD patients described a 5.3% rate of IA (Gu, 2021) https://pubmed.ncbi.nlm.nih.gov/33637057/ and a 2.14% in COPD patients admitted to hospital (Zhang, 2023) https://pubmed.ncbi.nlm.nih.gov/37302977/)

Mortality of IA in COPD Search: using the same search as above, all papers reviewed for overall and attributable mortality. The overall mortality of IA complicating COPD varies from 43% to 72% (Hammond, 2020; Gu, 2021), although Zhang (2023) found only a 4% mortality (English abstract only). Attributable mortality of IA in COPD can be derived from 3 studies. In a small case control study series Canada, those with IA had a 67% mortality, compared to only 7% in the matched controls (Muquim, 2005) https://pubmed.ncbi.nlm.nih.gov/16003456/ . In Spain, 48 patients with IA were compared with 70 COPD patients colonised with *Aspergillus*; mortality was 58.3% in those with IA compared with colonized patients (10.0%), an attributable mortality of 83-90% (Barberan, 2012) https://pubmed.ncbi.nlm.nih.gov/22863904/ . In China, comparing outcomes of those with a positive *Aspergillus* culture, those with IA had a 45% in-hospital mortality compared with colonised patients 0%, a 100% attributable mortality (Gu, 2021). At 180 days, crude mortality in those with IA had risen to 52.5% and in colonised patients to 6.7% (96.9% attributable) (Gu, 2021).

Intensive care beds and admissions. Search (Pubmed and Google): "intensive care" AND "global" OR "beds" OR "Capacity". In OECD 36 countries there are approximately 186,120 intensive (critical) care beds (14.1/100,000, population 1.32 Bn population) https://www.worlddata.info/alliances/oecd.php Multiple country papers (all available here: https://gaffi.org/media/country-fungal-disease-burdens/) have indicated intensive care beds in each country: Zhou (China) 86,000 in 2012 + Ray (India) 95,000 + Wahyuningsih (Indonesia) 7,094 + Giacomazzi (Brazil) 35,403 + Riera (Argentina) 9116 + Schwartz (South Africa) 4719 + Alvarez (Colombia) 2310 + Zurita (Ecuador) 781. This totals 426,543 critical care beds, and this figure is used for the total global number as a conservative figure, given that in many low resource countries the number of critical care beds is small.

The proportion of ICU bed admissions that are medical is estimated at 80% (341,234) and the median duration of stay 6 days (therefore 50 medical patients admitted per ICU bed per year) (20,758,400 globally). This arbitrary reduction in the total number of ICU beds to only medical ICU beds is also conservative, as IA can occur in surgical patients as well, but the duration of stay in surgical intensive care beds is usually much shorter.

Incidence of IA in intensive care. Search: "invasive aspergillosis" AND "intensive care" OR "ICU" Papers exclusively addressing influenza or COVID-19 were deselected. The range of incidence of IA in ICU patients varies from 1% to 5% (Papazian, 2020) https://pubmed.ncbi.nlm.nih.gov/32157357/ , the higher figures reflecting the use of pro-active diagnostic approaches (screening bronchoscopy and *Aspergillus* antigen detection) and probably the risk populations admitted to ICU. These figures do not specifically include patients with influenza, Covid-19 or severe fever with thrombocytopenia syndrome, which have a higher overall IA incidence (Denning, 2021) https://pubmed.ncbi.nlm.nih.gov/34183097/ . Invasive aspergillosis is a commonly missed diagnosis in ICU patients,based on autopsy studies (Maris, 2007 https://pubmed.ncbi.nlm.nih.gov/17252230/ ; Winters, 2012; https://pubmed.ncbi.nlm.nih.gov/22822241/ Tejerina, 2019 https://pubmed.ncbi.nlm.nih.gov/31177621/; Mudrakola, 2022 https://pubmed.ncbi.nlm.nih.gov/35633606/). Mean percentage developing IA is put conservatively at 2.5%. This is supported by a 25 year autopsy study from Spain which found 2.8% to have IA (Tejerina, 2019) A prospective 2 year survey of 38 intensive care units in 27 Italian hospitals, found a 6.31/1000 admissions to have IA (Tortorano, 2011) https://pubmed.ncbi.nlm.nih.gov/21668521/ . A prospective study of invasive mould infections in 11 ICUs in India found 7.8/1000 admissions to develop IA (using culture and bronchoalveolar lavage antigen diagnosis) (Chakrabarti, 2019) https://pubmed.ncbi.nlm.nih.gov/30769292/. In Turin, Italy *Aspergillus* was grown from the respiratory tract in 4.94/1000 ICU admissions with 66.6% probably having IA. Culture is ~40% sensitive for IA in ICU, so the likely incidence of IA was 8.2/1000 admissions (Corcione, 2021) https://pubmed.ncbi.nlm.nih.gov/33751395/ .

There is a possibility of duplication of IA incidence because of the underlying conditions linked to intensive care admission. For example in the autopsy study referred to above (Tejerina, 2019), the most common comorbid conditions in IA patients were corticosteroid treatment (n = 14, 56%), chronic obstructive pulmonary disease (COPD) (n = 11, 44%), immunosuppression (n = 6, 24%) and haematological malignancy (n = 5, 20%). Twenty-three patients (92%) had three or more risk factors for IA. This probable partial duplication has not been adjusted for given the conservative position taken on only including medical ICU beds, omission of influenza and Covid-19 cases and the overall affected figure of 2.5% applied.

Mortality of IA in ICU patients. Search: all the above papers were read for data and supplemented with search "aspergillosis" AND "ICU" AND "survival" and the same search with survival replaced by "mortality" There are multiple cohort and retrospective studies describing mortality of those with ICU in intensive care. Examples include data from Belgium a 28 day mortality of 49% and in hospital mortality of 77.1% (Vandewoude, 2006) https://pubmed.ncbi.nlm.nih.gov/16507158/ , also from Belgium a 66% ICU mortality (Meersseman, 2008) https://pubmed.ncbi.nlm.nih.gov/17885264/ , Italy a crude 30 day mortality of 63.1% (Tortorano, 2012), in the USA of 46% in patient mortality,

(Baddley, 2013) https://pubmed.ncbi.nlm.nih.gov/23343366/ , from India a 64.8% 6 week mortality (Chakrabarti, 2019) https://pubmed.ncbi.nlm.nih.gov/30769292/ , 67% in 30 ICUs in 8 high income countries (Taccone, 2015) https://pubmed.ncbi.nlm.nih.gov/25928694/ , in ICU mortality of 73% in a single tertiary care hospital in India (Dabas, 2018) https://pubmed.ncbi.nlm.nih.gov/29684057/ , 121 day crude mortality in a single Italian hospital of 82%, when all diagnoses were based on culture (Corcione, 2021).

Attributable mortality if IA in ICU Above papers reviewed for attributable mortality. Vandewoude and colleagues (2006) found an in-hospital mortality of 77.1% in 83 patients compared with 40.4% in colonised patients. A European observational study of IA in ICU patients found an overall mortality of 74% in 297 patients with IA compared to 38% of 266 colonised patients who were thought not to have IA (Taccone, 2015). This indicates an attributable mortality of ~51%.

IA in leukaemia and lymphoma Search: "invasive aspergillosis" AND each of the following terms separately "leukaemia", "lymphoma", "myelodysplastic syndrome", "multiple myeloma". IA in those with haematological malignancy, lymphoma, multiple myeloma, myelodysplastic syndrome and aplastic anaemia was calculated by taking the global leukaemia incidence in 2020 (474,519) https://gco.iarc.fr/today/data/factsheets/cancers/36-Leukaemia-fact-sheet.pdf and assuming 25% are acute myeloid leukaemia (weighted mean proportion 23.1%, regional range from 18.2-41.6% and rising) (Dong, 2020; https://ehoonline.biomedcentral.com/articles/10.1186/s40164-020-00170-6) (118,629) and that ~10% develop IA (Nicolle, 2011; https://pubmed.ncbi.nlm.nih.gov/21791468/ Koehler, 2017; https://pubmed.ncbi.nlm.nih.gov/27989379/ Van de Peppel, 2018; https://pubmed.ncbi.nlm.nih.gov/29727605/ Lien, 2018; https://pubmed.ncbi.nlm.nih.gov/29883443/ Chen, 2018; https://pubmed.ncbi.nlm.nih.gov/29449166/ Nganthavee, 2019; https://pubmed.ncbi.nlm.nih.gov/31165931/ Rodríguez-Veiga, 2019; https://pubmed.ncbi.nlm.nih.gov/31240471/ Martino, 2020 https://pubmed.ncbi.nlm.nih.gov/32564177/), and an equal number of other leukaemias and lymphomas, including multiple myeloma and myelodysplastic syndrome (37,962 cases) (Perkhofer, 2010 https://pubmed.ncbi.nlm.nih.gov/20947312/ ; Lortholary, 2011; https://pubmed.ncbi.nlm.nih.gov/21668573/ ; Chen, 2020; https://pubmed.ncbi.nlm.nih.gov/29449166/).

IA in allogeneic HSCT Search (Pubmed and Google): "Allogeneic haematopoetic stem cell transplant" AND "global" or "worldwide" or given years, 2017, 2018, 2019, 2020, 221, 2022. In 2016, the Worldwide Network of Blood and Marrow Transplantation (WBMT) reported 38,425 allogeneic haematopoetic stem cell transplants (alloHSCT) (including family and unrelated donor transplants) (https://pubmed.ncbi.nlm.nih.gov/34382386/). This an 88% increase on 2016, and so the anticipated number of alloHSCT procedures in 2021 is ~55,000 globally. The annual incidence of IA in these patients varies by era of transplantation Higher IA rates in pre-2010 cohorts), diagnostic use of galactomannan, use of prophylaxis, adult or paediatric and concomitant viral infection or not, as well as the rate of grade 2-4 graft versus host disease (GVHD). In more recent data, Nucci et al reported a 3.3% rate in 378 alloHSCT patients in Brazil (2007-2009) (https://pubmed.ncbi.nlm.nih.gov/23009319/); The GITMO group in Italy reported a 7.1% of IA in 1858 patients transplanted from 2008-2010 (https://pubmed.ncbi.nlm.nih.gov/24631738/); from China, Sun and colleagues found a 3.0% rate of IA in alloHSCT in 2011 in 1053 patients (https://pubmed.ncbi.nlm.nih.gov/25840339/); in a children's hospital in Argentina, the rate of IA was 2.2% in 143 alloHSCT recipients from 1998-2016 (https://pubmed.ncbi.nlm.nih.gov/29679436/); and in Germany also in children from 2005-2015, the IA rate was 5.1% after 221 first procedures (https://pubmed.ncbi.nlm.nih.gov/31661569/); in 71 alloHSCT patients in Brazil (2015-2016), the rate of IA was 5.5% (https://pubmed.ncbi.nlm.nih.gov/33141969/); 6% rate in 53 Australian children after alloHSCT (2004-2013) (https://pubmed.ncbi.nlm.nih.gov/30511385/); in Taiwan, 4.5% occurred in 245 adults following alloHSCT (2003-2014) (https://pubmed.ncbi.nlm.nih.gov/30322746/); among 479 alloHSCT recipients in Switzerland from 2009-2013, 6.0% developed IA (https://pubmed.ncbi.nlm.nih.gov/30144374/); in Austria from 2009-2013, 242 adult recipients of alloHSCT, 7.4% developed IA (https://pubmed.ncbi.nlm.nih.gov/26715563/); and in USA, of 378 alloHSCT patients (2002-2011), 8.2% developed IA (https://pubmed.ncbi.nlm.nih.gov/25808822/). Here a rate of 6% has been used.

Mortality of IA in acute leukaemia. Search: "invasive aspergillosis" AND "leukaemia" AND "Survival" and the same search repeated replacing survival with "mortality". In France, 127 developed IA complicating leukaemia and 42% died at 3 months, slightly decreasing over the period 2008-2009 (Nicolle, 2011). https://pubmed.ncbi.nlm.nih.gov/21791468/ Among 55 patients in Korea with IA complicating haematological disease, crude mortality was 38.9% and attributable mortality 33.3% (86% attributable) (Kwon, 2012) https://pubmed.ncbi.nlm.nih.gov/23227068/. In a large study in Germany the crude mortality at 12 weeks was 33.8% and attributable mortality 26.9% (Koehler,

2017). Of 102 patients with haematological malignancy, positive cultures for A. fumigatus and IA, 36% died (Heo, 2017) https://pubmed.ncbi.nlm.nih.gov/28379304/. In a large retrospective series form a cancer centre in the USA, among 340 patients with IA, the crude mortality was 38.8% and attributable 33.8% (87% attributable) (Dib, 2018) https://pubmed.ncbi.nlm.nih.gov/30545320/ In seven centres in Brazil, the 6 and 12 week mortality of adults with AML was 37% and 48.1% and for ALL was 43.5% and 56.5% respectively (Colombo, 2023 https://pubmed.ncbi.nlm.nih.gov/36316599/). A meta-analysis and systematic review of 49 publications with cohort sizes of >50 depicting results in 1056 patients with IA in leukaemia and after haematopoetic stem cell transplantation (HSCT) found a crude fatality rate (CFR) at 100 days of 29% (Van de Peppel, 2018). The authors separated out groups into acute leukaemia without prophylaxis (CFR 30.3%), allogeneic HSCT with antifungal prophylaxis (CFR 12.0%), allogeneic HSCT without antifungal prophylaxis (CFR 45%) and mixed populations treated for haematological malignancy (CFR 19%). Here we use an overall mortality of 45%, to allow for many units in LMICs not using antifungal prophylaxis and other limitations in care. Although slightly higher mortality is seen in alloHSCT patients with IA than in AML, these procedures are done primarily in high income countries, where AML IA mortality is slightly lower. For this reason the mortality estimate for alloHSCT patients with IA is maintained at 45%. Extremely few patients with IA in leukaemia survive without antifungal therapy, hence an untreated mortality of >95%, in reality probably close to 100%, and an attributable mortality estimated at ~80%, to account for some unresponsive leukaemias and other complications leading to death. IA often delays cycles of chemotherapy, with worse leukaemia outcome, even if IA is subsequently not the cause of death (Candoni, 2020) https://pubmed.ncbi.nlm.nih.gov/32697010/.

Lung cancer incidence Search (Pubmed and Google) "Incidence" AND "lung cancer" and again with lung cancer replaced by 'Carcinoma of the lung" The total annual global incidence of lung cancer in 2020 (2,206,771) is taken from the International Agency for Research in Cancer https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf The Global Burden of Disease consortium estimated 2,260,000 incident cases of carcinoma of the trachea, bronchus or lung in 2019 (Kocarnik, 2022 https://pubmed.ncbi.nlm.nih.gov/34967848/). We have used the smaller 2020 figure in our estimates. Multiple small series attest to the mis-diagnosis of fungal lung disease (including aspergillosis) as lung cancer (Yoon, 2011; https://pubmed.ncbi.nlm.nih.gov/21596796/ Baxter, 2011; https://pubmed.ncbi.nlm.nih.gov/21460371/ Schweigert, 2013; https://pubmed.ncbi.nlm.nih.gov/22592566/ Guinmaraes, 2013 https://pubmed.ncbi.nlm.nih.gov/24043490/ ; Dermawan, 2020 https://pubmed.ncbi.nlm.nih.gov/31743469/). A large Danish series of suspected lung cancer cases found chronic pulmonary aspergillosis to be the correct diagnosis in 16/992 (1.6%) (Ronberg, 2022) https://pubmed.ncbi.nlm.nih.gov/35330299/ .

IA in lung cancer Search "aspergillosis" AND "lung cancer" and again with lung cancer replaced by 'Carcinoma of the lung". Search repeated on November 2nd 2023. Yan et al (2009) https://pubmed.ncbi.nlm.nih.gov/19637340/ in Chengdu, China assessed IA as a complication of 1711 patients with proven lung cancer and found 45 (2.6%) to have their clinical course complicated by IA. Many had been treated with corticosteroids and had concurrent morbidities and other infections. Others have documented IA in lung cancer patients. In Aligarh, India Malik and colleagues (2003) https://pubmed.ncbi.nlm.nih.gov/15025326/ detected *Aspergillus* in bronchoalveolar lavage in 6 of 42 patients (14%) with bronchogenic carcinoma and serological evidence of *Aspergillus* in 9 (21%). Ali et al (2014) https://pubmed.ncbi.nlm.nih.gov/24771735/ (also in Aligarh) found 23 of 45 (51%) patients with *Aspergillus* detected in bronchoscopy samples to have IA, but denominators are missing. Park et al, (2020) https://pubmed.ncbi.nlm.nih.gov/33168426/ found 32 cases of pulmonary aspergillosis or cryptococcosis among 5280 (0.6%) in the USA, of which 12 were proven or probable. A cancer registry series in Taiwan using iCD9 coding, found 100 of 122,801 (0.08%) patients with lung cancer In Taiwan to have aspergillosis, with an increasing trend from 2006 to 2017 (Chen, 2022) https://pubmed.ncbi.nlm.nih.gov/35859914/. Kuo (2023) sought invasive aspergillus with serum or BAL galactomannan in 290 of 2543 lung cancer cases diagnosed between 2013 and 2021 and found 34 (11.7%) to be positive (1.3% of all) https://pubmed.ncbi.nlm.nih.gov/37720497/ .

Mortality of IA complicating lung cancer Analysis of the above papers for overall and attributable mortality Yan et al found an overall mortality of, 51%, most (74%) dying within one month of IA diagnosis, almost all of whom were treated with itraconazole. A small US series showed apparent progressive lung cancer to actually be opportunistic IA, 83% died, 20% attributed to IA, 70% attributed to lung cancer and 10% to both IA and lung cancer (Park, 2020). A US series of solid tumour cases complicated by invasive aspergillosis (37% lung cancer) found an overall 33% 12 week mortality, of which 50% was attributable (Dib, 2020) https://pubmed.ncbi.nlm.nih.gov/31585141/. In Taiwan, 77% of patients with IA and lung cancer died contrasting with 74.3% in this not diagnosed with aspergillosis (Chen, 2022). In Kaplan-Meier survival analyses, invasive aspergillosis was associated with a 4 month shorter survival time (9.9 months versus 14.4 months) and a median 1.9 months from invasive aspergillosis diagnosis to death; ~65% had died within 3 months, compared to ~48% of those without aspergillosis (Kuo, 2023). We have assumed a 51% treated mortality and 40% attributable mortality.

Chronic pulmonary aspergillosis incidence. No additional searches were done to augment the paper summarised below. Previous estimates of CPA estimated only cases occurring after pulmonary tuberculosis (TB) treatment was successfully completed. A recent estimate of CPA related to pulmonary tuberculosis in 2019 in India (the country with the largest burden of TB globally) added cases which are 1) mis-diagnosed as pulmonary TB, 2) co-infections of TB and CPA and 3) cases occurring during the first year after TB diagnosis (Denning, 2022) https://pubmed.ncbi.nlm.nih.gov/36568568/ . This new estimate found a 2019 annual incidence of CPA arising in PTB patients of 363,601 cases (range 254,521 – 472,682), 17.5% of the total PTB cases presenting for care. The 5-year period prevalence of CPA was estimated at 1,575,716 which raised the CPA prevalence estimate for India in 2014 from 290,000 to >1.5 million. The inclusion of cases mis-diagnosed and occurring early in the treatment course of pulmonary TB had a major impact on both incidence and prevalence.

A global model of CPA prevalence occurring at least one year after pulmonary TB was published in 2013 (Denning, 2011) https://pubmed.ncbi.nlm.nih.gov/22271943/ and ~1.2 million affected was estimated. Applying this new model (Denning, 2022) from India globally, using 2020 WHO pulmonary TB estimates assumes a global incidence of pulmonary TB of 8,093,400 cases, of which 645,340 are co-infected with HIV and overall, 41% are clinically diagnosed without laboratory confirmation. In that year deaths from pulmonary TB were estimated to be 1,049,600 in HIV-negative and 175,480 in HIV-positive people. The outputs of this model show an incidence of new CPA cases from newly present 'TB' cases of 1,390,766 cases (with 153,029 deaths, 12.5% of the overall TB deaths). In addition, 446,505 new CPA cases are estimated to present in 2020 in survivors of pulmonary TB from the previous 5 years, a 2020 CPA incidence of 1,837,271 new cases.

CPA is a chronic disease with substantial morbidity as well as mortality. Once deaths have been factored in, the overall CPA global prevalence related to, or mis-diagnosed as, pulmonary TB is approximately 6,100,000 (using 2 estimation approaches) (Denning, 2022). Here we only present the annual incidence estimate of 1,837,271, omitting the additional later cases of CPA of ~4,303,800 cases.

Mortality from CPA. Data were extracted from the paper above and all references detailing mortality over time are summarised there. A summary of all 26 CPA cohort studies from multiple centres and countries found the mortality of CPA to be 20% (range 0-40%) in the first year after presentation and 7.5% annually thereafter over 5 years to yield a five year mortality of 50% (range 16.4% to 80%) (Denning, 2022). There were mostly treated patients, although the diagnosis was made late in many. Antifungal therapy is partially effective in reducing morbidity and probably mortality. It is ~60% effective, so we assume an annual survival benefit estimated at 12% annually (60% reduction of the expected 20% mortality). We would expect this benefit to continue in future years for most patients, but have not applied it beyond year 1. There are fewer data on untreated patients and large divergences, possibly related to corticosteroid administration (which increases mortality by 2.74 fold (Li Z et al, 2023) https://pubmed.ncbi.nlm.nih.gov/36852004/ and either or both of co-infection and different co-morbidities.

The documented 5-year mortality is~ 50% in patients mostly treated with antifungal therapy (Denning, 2022). To illustrate this, the modelling in India estimated 42,766 deaths (range 29,936–55,595) in newly occurring CPA cases, 10.5% of total PTB deaths. An additional 100,715 CPA deaths (range 70,500 – 130,930) were estimated from all cases, an annual estimated total of was 143 481 (range 100 436 – 186 525). A significant weakness of these data is that most mortality estimates are from high income countries with affected patients predominantly 55-70 years old. The average age of pulmonary TB is 10-15 years younger, and the outcomes could be different. Here we only include the 20% mortality in the first year after developing CPA. We have applied this globally, assuming that fewer than 1 in 10 CPA diagnoses are currently made.

Attributable mortality of CPA The papers detailing mortality from Denning, 2022 were re-read to identify those that separately described crude and attributable mortality. Search: "chronic pulmonary aspergillosis" AND "attributable mortality". Rafferty in 1983 followed up 20 patients with an aspergilloma, of whom 12 died, 5 attributable to CPA (attributable 38.5%). In Japan, of 21 deaths, 18 (85.7%) were attributed to CPA (Ohba, 2012) https://pubmed.ncbi.nlm.nih.gov/22349065/ . In 41 patients with CPA and sub-acute IA prospectively treated with antifungal therapy, five died (12.2%) within 12 months, none attributable to aspergillosis (Cadranel, 2012) https://pubmed.ncbi.nlm.nih.gov/22782438/ . In South Korea, among 88 deaths in CPA patients, CPA was the apparent cause of death in 26.1% (Jhun, 2013) https://pubmed.ncbi.nlm.nih.gov/23834282/. Among 21 CPA patients in Italy, 7 (33.3%) died all attributed to underlying disease or in one case an accident (Cucchetto, 2015) https://pubmed.ncbi.nlm.nih.gov/25432571/ . In Brazil, among 21 patients with significant haemoptysis and CPA treated with lung radiotherapy, nine patients died, two directly related to CPA (attributable mortality 22.2%) (Sapienza, 2015) https://pubmed.ncbi.nlm.nih.gov/26612361/ . In a large series of fibrocystic sarcoidosis in France, followed up for a mean of 7 years, Uzunhan (2017) diagnosed 65 patients with CPA of whom 41.5% died, a 73% five year survival https://pubmed.ncbi.nlm.nih.gov/28619957/ . They attributed most deaths to progressive pulmonary sarcoidosis, with 3 deaths (4.8%) directly due to CPA. There is uncertainty about the role of CPA in contributing to pulmonary fibrosis and premature death in these patients. Among 387 patients with CPA in the UK, CPA was listed either in causal sequence to death or contributing towards death in 27 (67.5%) patients (Lowes, 2017) https://pubmed.ncbi.nlm.nih.gov/28179437/ . Three (7.5%) patients died of conditions unrelated to CPA. Ten (25%) other deaths were attributed to COPD or sarcoidosis, and it is uncertain if CPA was a contributory factor. In Japan, there were 22 of 62 (35.5%) in patients with CPA and non-tuberculous pulmonary infection and 17 were attributed to the infections (77.3% attributable) (Naito, 2018) https://pubmed.ncbi.nlm.nih.gov/29764749/ . In a select group of patients with CPA and significant haemoptysis, 8 of 14 (57%) were attributable to CPA (Ando, 2019) https://pubmed.ncbi.nlm.nih.gov/30692051/ . Aguilar-Company in Spain do provide data on attributable mortality but only with CPA with merged with sub-acute IA (2019) https://pubmed.ncbi.nlm.nih.gov/31162731/ .

Incidence of *Candida* bloodstream infection After summarising all the individual country estimates listed below (which were comprehensive at the time of writing, and included any grey literature) and in supplementary data 2, searches of 'candidemia' AND each individual country was done adjusted by date to capture any new data published after the papers below, Individual country estimates were summed from individual country burden papers or abstracts published from 2013-2023 (see https://gaffi.org/media/country-fungal-disease-burdens/ (summarised in Suppl. 2 of this article). Variations within country can be large, as shown by a study in Belgium which found candidaemia incidence rates differed up to 20-fold among 30 Belgian hospitals without any obvious explanation (Trouve, 2016) https://pubmed.ncbi.nlm.nih.gov/27858242/ Country estimates without local data were assumed to be 5/100,000. The published estimates are as follows: Algeria 2272 (5.2/100,000) (Aissat, 2023), Argentina 2193 (5.0/100,000) (Riera, 2018), Austria 209 (2.6/100,000) (Lass-Florl, 2016); Australia 440 (1.9/100,000) (Chen, 2014); Azerbaijan 499 (5/100,000) (Huseynov, 2021); Bangladesh 8100 (5/100,000) (Gugnani, 2017); Belarus 478 (5/100,000) (Skrahina, 2017); Belgium 555 (5/100,000) (Lagrou, 2015); Brazil 28,991 (14.9/100,000) (Giacomazzi, 2016); Burkina Faso 906 (5/100,000) (Bamba 2018); Cameroon 1113 (5/100,000) (Mandangue, 2018); Canada 1034 (2.91/100,000) (Dufresne, 2017); Chile 878 (5/100,000) (Duarte, 2017); China 82,011 (5.72/100,000) (Zhou, 2020); DRC 4470 (5/100,000) (Kamwiziku, 2021); Congo (Republic of) 260 (5/100,000) (Amona, 2020); Colombia 6296 (12.8/100,000) (Alvarez-Moreno, 2018); Cote d'Ivoire 1260 (5/100,000) (Koffi, 2021); Czechia 526 (5/100,000) (Chrdle, 2015); Denmark 527 (9.4/100,000) (Mortensen, 2015); Dominican Republic 136 (5/100,000) (Gugnani, 2015); Ecuador 1037 (7.2/100,000) (Zurita, 2017); Egypt 4127 (5/100,000) (Zaki, 2017); Eritrea 177 (5/100,000) (Werkneh, 2022); Ethiopia 5300 (5/100,000) (Tufa, 2019); France 2370 (3.6/100,000) (Gangneux, 2016; Bretagne, 2022); Germany 3712 (4.6/100,000) (Ruhnke, 2015); Ghana 541 (5/100,000) (Ocansey, 2019); Greece 541 (5/100,000) (Gamaletsou, 2016); Guatemala 772 (5/100,000) (Medina, 2017); Honduras 495 (5/100,000) (Agudelo Higuita, 2022); Hungary 1110 (11/100,000) (Sinko, 2015); India 188,035 (13.5/100,000) (Ray, 2022); Indonesia 26,710 (10/100,000) (Wahyningsih, 2021); Iraq 1850 (5/100,000) (Karzan, unpublished); Iran 3996 (5/100,000) Hedayati, 2019); Ireland 403 (6.3/100,000) (Dorgan, 2015); Israel 649 (8.13/100,000) (Ben-Ami, 2015); Italy 13,351 (21.8/100,000) (Bassetti, 2017); Jamaica 136 (5/100,000) (Gugnani, 2015); Japan 6350 (5/100,000) (Izumakawa, 2016); Jordan 316 (5/100,000) (Wadi,2018); Kazakhstan 765 (4.3/100,000) (Kemaikin, 2018); Kenya 2804 (5/100,000) (Ratemo, 2023); South Korea 1976 (4.3/100,000) (Huh, 2017); Kuwait 288 (6.8/100,000) (Alfouzan, 2020); Kyryzstan 250 (4.2/100,000) (Turdumambetova, 2019); Madagascar 981 (5/100,000) (Rakotoarivelo, 2015); Malawi 750 (5/100,000) (Kalua, 2018); Malaysia 1533 (5/100,000) (Velayuthan, 2018); Mali 1063 (5/100,000) (Doumbo, 2023); Mexico 5617 (5/100,000) (Corzo-Leon, 2015); Mongolia 141 (5/100,000) (Battur, 2013); Morocco 1830 (5/100,000) (Lmimouni 2022);Mozambique 1321 (5/100,000) (Sacarlal, 2018); Namibia 125 (5/100,000) (Dunaiski, 2019); Nepal 1365 (5/100,000) (not previously estimated); Netherlands 445 (2.6/100,000) (Buil, 2020); Nigeria 9284 (6.0/100,000) Oladele, 2014); Norway 200 (3.8/100,000) (Nordoy, 2018); Oman 265 (5/100,000) (Al-Hatmi, 2020); Pakistan 38,745 (21/100,000) (Jabeen, 2017); Panama 220 (5/100,000) (Rodriguez-Vargas, 2023, in press); Paraguay 348 (5/100,000) (Aguilar, 2019); Peru 1557 (5/100,000) (Bustamante, 2017); Philippines 1968 (2/100,000) (Batac, 2017); Portugal 231 (2.2/100,000) (Sabino, 2017); Qatar 288 (15.4/100,000) (Taj-Aldeen, 2015); Romania 984 (5/100,000) (Mares, 2018); Russia 9558 (6.7/100,000) (Klimko, 2015); Senegal 700 (5/100,000) (not previously estimated); Serbia 518 (7.3/100,000) (Arsenijevic, 2018); Sierra Leone 383 (5/100,000) (Lakoh, 2021); Singapore 267 (5/100,000) Lum, 2013); South Africa 5421 (9.6/100,000) (Schwartz, 2019); Spain 3807 (5/100,000) (Rodriguez Tudela, 2015); Sri Lanka 507 (2.53/100,000) (Jaysakera, 2015); Sudan 2304 (5/100,000) (Ahmed, 2023); Sweden 471 (4.7/100,000) (Ozenci, 2019); Taiwan 861 (3.68/100,000) (Huang, 2019); Tajikistan 371 (4.2/100,000) (Bobokhojaev, 2019); Tanzania 2181 (5/100,000) (Faini, 2015); Thailand 8650 (13.3/100,000) (Chayakulkeeree, 2017); Togo 363 (5/100,000) (Dorkenoo, 2021); Trinidad and Tobago 70 (5/100,000) (Edwards, 2021); Tunisia 586 (5/100,000) Fathallah (manuscript in preparation); Turkey 3847 (4.76/100,000) (Hilmioglu-Polat, 2018); Uganda 2293 (5/100,000) (not

previously estimated); Ukraine 2278 (5/100,000) (Osmanov, 2015); United Kingdom 5142 (3.1/100,000) (Pegorie, 2017); United States of America 19,920 (6.1/100,000) (Rayens, 2022) and 22,660 (7/100,000) (Tsay, 2020) (the higher figure is used as not subject to incorrect coding); Uruguay 565 (16.4/100,000) (Macedo-Vinas, 2018); Uzbekistan 1825 (5.93/100.000) (Tilavberdiev, 2017); Venezuela 4,798 (16/100,000) (Dolande, 2015); Vietnam 11,291 (11.7/100,000) (Duong, 2023); Zambia 550 (5/100,000) (Chishimba 2013); Zimbabwe (743 (5/100,000) (Pfavayi, 2021). No adjustment was made for missing countries, as most are low or low-middle income countries and their collective population is <10% of the global population not covered above.

Mortality of *Candida bloodstream infection*. Search: "candidemia" AND "Survival" and the same search repeated replacing survival with "mortality". Mortality rates are presented in the literature at different time points after diagnosis, some at 7 days, some at 30 days, some at 90 days and some describe mortality in intensive care or at hospital discharge, which may be to another healthcare facility, where the eventual outcome is not captured. Generally the 30 day mortality is most often given, which is what is used for estimation here. We have summed the overall mortality in adults and children at 35%, with a wide range.

Overall mortality rates in the literature are many. Among 419 patients with candidaemia in Spain, 37% died in 30 days (Fortun, 2012) https://pubmed.ncbi.nlm.nih.gov/22369861/ In the UK a case-control study of candidaemia (2003-2007) found an overall 45.8% crude mortality of primarily ICU patients (Hassan, 2009) https://pubmed.ncbi.nlm.nih.gov/19744519/ . in South Africa, from 1990 to 2007 the crude mortality was 60%, without any trend showing improvement (Kreusch, 2013) https://pubmed.ncbi.nlm.nih.gov/23535300/ In Paris ICU patients from 2002-2010 mortality increased to 56.9% overall (Lortholary, 2014) https://pubmed.ncbi.nlm.nih.gov/25097069/ . A population-based analysis of candidaemia and its mortality from 2001-2010 found a 40% overall in-hospital mortality (Bitar, 2014) https://pubmed.ncbi.nlm.nih.gov/24960557/ . A 54% 30 day mortality was observed in those with septic shock and candidaemia in 5 hospitals in Spain and Italy (Bassetti, 2014) https://pubmed.ncbi.nlm.nih.gov/24807083/ . In Beijing, China, overall mortality was 58.5% (Zhong, 2015) https://pubmed.ncbi.nlm.nih.gov/26178355/ . In Colombia, in-hospital crude mortality was 35.9% (Cortez, 2014) https://pubmed.ncbi.nlm.nih.gov/25181401/ . In Turkey, the crude mortality rate among candidemia cases was 30% from 2009-2011 (Karadag, 2016) https://pubmed.ncbi.nlm.nih.gov/28081316/ In adults in Italy more than 74 years old the mortality of *Candida* bloodstream infection was 47.8% compared to 23.6% younger adults (Zatta, 2020) https://pubmed.ncbi.nlm.nih.gov/33070136/ A similar finding in Spain found a 30-day mortality of 42% in those patients over 75 years old (Ramos-Martinez 2017) https://pubmed.ncbi.nlm.nih.gov/28836309/ In Texas, USA (2001-2010) in hospital mortality was 23.8% (Oud, 2016) https://pubmed.ncbi.nlm.nih.gov/26985250/ and 29.8% in-hospital mortality was observed over the years 2002-2015 in Missouri (Mejia-Chew, 2019) https://pubmed.ncbi.nlm.nih.gov/31562024/ . The 30 day mortality in 12 hospitals in Spain and Italy was 22% (Bassetti, 2020 https://pubmed.ncbi.nlm.nih.gov/32216822/ A 30-day mortality of 31.7% from candidemia was documented in in Santiago, Chile (Siri, 2017) https://pubmed.ncbi.nlm.nih.gov/28394977/ In Pakistan in cancer patients from 1195-2013, 53.4% died with any clear improvement trend over time. (Raza, 2016) https://pubmed.ncbi.nlm.nih.gov/27183941/ a 23.1% mortality in 410 major burn patients with candidaemia in Chongqing, China (Zhou, 2019) https://pubmed.ncbi.nlm.nih.gov/30686692/ 100 cases of candidaemia between 2014 and 2017, overall mortality was 43% and 30 day mortality 38% (Cornely 2020) https://pubmed.ncbi.nlm.nih.gov/32885534/. The 30 day mortality in 12 hospitals in Spain and Italy was 22% (Bassetti, 2020 https://pubmed.ncbi.nlm.nih.gov/32216822/. In Cologne, Germany among 57 patients, the in-hospital mortality was 33.3%, and 30 day mortality 23.5% (Blankenheim 2021) https://pubmed.ncbi.nlm.nih.gov/34847247/ . A 24.2% 12 week mortality in adults with acute lymphocytic leukaemia was seen in France (Mariette, 2017) https://pubmed.ncbi.nlm.nih.gov/27397551/ In Colombia, a crude mortality at 30 and 90 days of candidemia of 37.8% and 40.5% respectively (Alvarez-Moreno, 2023)

https://pubmed.ncbi.nlm.nih.gov/37108885/ A review including published articles depicting the characteristics and crude mortality of *Candida auris* infection to July 2017 found 33.3-100% mortality from 11 countries (Sekere, 2017). In the USA, the crude mortality of *Candida auris* and other species of *Candida* causing bloodstream infection of 30.1% and 38.9% respectively (Simon, 2023). https://pubmed.ncbi.nlm.nih.gov/36062367/. In Pakistan, crude mortality was 42.4% in patients with *C. auris* bloodstream infection (Sayeed, 2019) https://pubmed.ncbi.nlm.nih.gov/31060514/ . In the USA, in-hospital mortality was 28.8% in 163 patients, and 30 day mortality was 31.3% (Steuber, 2021) https://pubmed.ncbi.nlm.nih.gov/33387121/ In Australia an eight centre study found a 31% all cause mortality at 30 days (Keighley, 2019) https://pubmed.ncbi.nlm.nih.gov/31113382/ In Japan, between 2002 and 2013, the overall 30-day and 180-day all-cause mortality were 23.7% and 47.0% respectively (Ishikane, 2019) https://pubmed.ncbi.nlm.nih.gov/31022251/ In five regional hospitals in Japan between 2011 2016, overall 30-day mortality of candidaemia was 27.7% (Kato, 2019) https://pubmed.ncbi.nlm.nih.gov/30718191/ In a small series from Turkey, the mortality was 83.3% in ICU (Tigen 2017) https://pubmed.ncbi.nlm.nih.gov/28359611/ In Italy, the overall 30 day mortality was 31.8% among 213 patients (Murri, 2018) https://pubmed.ncbi.nlm.nih.gov/29742466/ . In adult ICUs in Saudi Arabia, the in-hospital mortality was 58.6% (Al-Dorzi, 2020) https://pubmed.ncbi.nlm.nih.gov/29628014/ The 10-day mortality was 32.2% in 10 Turkish medical centres (Dogan, 2020) https://pubmed.ncbi.nlm.nih.gov/32335275/ In Liaoning, China, the 30-day mortality of candidaemia in surgical patients was 19.2% (Zhang, 2020) https://pubmed.ncbi.nlm.nih.gov/32660641/ In Shanghai, China, the 28 day mortality was 28.5% (Zheng, 2021) https://pubmed.ncbi.nlm.nih.gov/33985505/ In Turkey, the overall 30-day mortality was 56.7% (Kutlu, 2022) https://pubmed.ncbi.nlm.nih.gov/35083558/ In Brazil in ICU patients mortality was 77.3% (Hohmann, 2023) https://pubmed.ncbi.nlm.nih.gov/36659829/ In New York, USA, the 30-day crude mortality of 292 cancer and transplant recipients with non-albicans candidaemia was 40% (Otto, 2023) https://pubmed.ncbi.nlm.nih.gov/37365379/.

In children, mortality from *Candida* bloodstream infection is usually 10-20%, slightly higher in premature neonates at ~20%. In South Africa, overall mortality was 45.8% (Ballot, 2013) https://pubmed.ncbi.nlm.nih.gov/23803724/ . In a large children's hospital in Ankara, Turkey, 28.6% died within 30 days of diagnosis of candidaemia (Karadag-Oncel, 2015) https://pubmed.ncbi.nlm.nih.gov/25678411/ In the UK in 14 neonatal units from 2004-2010, 84 cases of Candida bloodstream infection resulted in an overall mortality of 31% (Oeser, 2014) https://pubmed.ncbi.nlm.nih.gov/24479862/ in 12 years in China, 42.7% of 96 neonates and 25.4% of children died of Candida bloodstream infection (Hsu, 2018) https://pubmed.ncbi.nlm.nih.gov/29699503/ in another 3 year study 2009-2011 in 11 units, 223 developed invasive candidiasis (96% with a positive blood culture) and 19.2% died (Xia, 2013) https://pubmed.ncbi.nlm.nih.gov/24153006/; in 3 hospitals in Iran, 109 children developed candidaemia and 40% died. Ahangarkani https://pubmed.ncbi.nlm.nih.gov/31985076/ among 53 children with candidaemia and cancer in Turkey, the 30 day mortality was 11.3% (Duzgol, 2022) https://pubmed.ncbi.nlm.nih.gov/34486572/ In cardiac surgery cases in Israel, 35 cases of candidaemia were seen over 16 years to 2019 and 28.5% died. Kahan, https://pubmed.ncbi.nlm.nih.gov/36854105/ in Taiwan, Wang et al (2023) describe 95 episodes of candidaemia with a crude mortality of 33% https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10221353/ ; also in Taiwan, among 319 children with candidaemia, 23.5% died within 30 days (Lee, 2018) https://pubmed.ncbi.nlm.nih.gov/30100260/ In another large series from Taiwan, over 13 years, mortality from candidaemia at 7 and 30 days was 13.4% and 25.2%, and overall in-hospital mortality 35.1%. (Tsai, 2017) https://pubmed.ncbi.nlm.nih.gov/28439070/ In Kobe, Japan, 26 children developed candidaemia and 23% died (2019) Kishimoto https://pubmed.ncbi.nlm.nih.gov/31011987/ an overall mortality of 42.4% in 66 children in Egypt (Hegazi, 2014) https://pubmed.ncbi.nlm.nih.gov/24820467/. Among 34 children with *C. auris* candidaemia in Colombia, 41% died (Berrio, 2021) https://pubmed.ncbi.nlm.nih.gov/32373928/ In

129 children in Saudi Arabia, with candidaemia, 36.4% died (Almoosa, 2017) https://pubmed.ncbi.nlm.nih.gov/29114700/ In 69 premature infants in China 8.7% died (Fu, 2018) https://pubmed.ncbi.nlm.nih.gov/28477628/ In Brazil, 32% of children with candidaemia died (Motta, 2017) https://pubmed.ncbi.nlm.nih.gov/27712962/ In Victoria, Australia, the overall mortality was 12% (Silvester, 2021) https://pubmed.ncbi.nlm.nih.gov/33591077/ In Brazil, among 94 children with candidaemia, including some in the neonatal ICU, mortality was 14% (Rodrigues, 2019) https://pubmed.ncbi.nlm.nih.gov/31169713/

Attributable mortality of *Candida* bloodstream infection. Search: "candidemia" AND "attributable mortality". The above papers were checked for separation of attributable from crude mortality. In severely burned patients, the crude mortality of candidemia was 23.1%, and the mortality attributable to candidemia was 15% (65%); Zhou https://pubmed.ncbi.nlm.nih.gov/30686692/ In Spain, ICU patients with and without candidemia had a crude mortality of 52.6% versus 20.6% in those without (57%) (Gonzalez de Molina2012) https://pubmed.ncbi.nlm.nih.gov/22698004/ Chakrabarti 2015, An attributable mortality of 88% in adults with ALL in France (Mariette, 2017) https://pubmed.ncbi.nlm.nih.gov/27397551/ In premature neonates in the UK, the overall mortality was 31% and attributable mortality 21%. In China, all 19.2% deaths were attributed to Candida infection (100%) (Xia, 2013) https://pubmed.ncbi.nlm.nih.gov/24153006/ In non-neonatal candidiasis in children, the overall mortality was 42.4% and attributable of 16.7% in Egypt (61%) (Hegazi, 2014) https://pubmed.ncbi.nlm.nih.gov/24820467/, Of 53 children in Taiwan with candidaemia 33% died with an attributable mortality of 24.2% (73%). in 3 hospitals in Iran, 109 children developed candidaemia and 40% died, 48% of them attributable to this infection Ahangarkani https://pubmed.ncbi.nlm.nih.gov/31985076/ 26 children developed candidaemia and 23% died, and the attributable mortality was 12% (52%) (Kishimoto, 2019) https://pubmed.ncbi.nlm.nih.gov/31011987/ In Cologne, Germany among 57 patients, the in-hospital mortality was 33.3% and attributable 21.5% (65%) and 30 day overall mortality 23.5% and attributable mortality 15.7% (67%) (Blankenheim 2021) https://pubmed.ncbi.nlm.nih.gov/34847247/ In cologne, the attributable mortality was 26-27% compared with 43% (60%) and 38% (71%) overall mortality ((Cornely 2020) https://pubmed.ncbi.nlm.nih.gov/32885534/). In a case-controlled study in the UK, the crude mortality of candidaemic patients was 45.8% with a control mortality of 11.1% (76%) (Hassan, 2009). In Cologne, in-hospital-mortality in those with candidaemia was 33.3% and 11.8% in controls, giving an attributable mortality rate of 21.5% (65% attributable) (Blankenheim, 2022). In Brazil in ICU the mortality of candidaemia was 77.3% in cases and 11.9% in controls, an attributable mortality of 84.6% (Hohmann, 2023) https://pubmed.ncbi.nlm.nih.gov/36659829/ In Turkey, a case control comparison found an 83.3% mortality in cases and 45.9% in controls, a 44.9% attributable mortality (Tigen 2017) https://pubmed.ncbi.nlm.nih.gov/28359611/

Incidence of invasive candidiasis, including intraabdominal and peritoneal candidiasis, without a positive blood culture. Searches: "invasive candidiasis" AND "incidence" and "peritoneal candidiasis" AND "incidence", removing all series where bloodstream infection was not clearly separated from cases where blood cultures were negative. Several studies attest to the insensitivity of blood culture to diagnose invasive candidiasis, which may affect a single organ, or be disseminated. In decades past the primary comparator was autopsy; in recent decades the development of non-culture biomarkers has allowed other estimates of the performance of blood culture. Antifungal prophylaxis reduces the sensitivity of blood culture, especially for *Candida albicans* (Kami, 2002) https://pubmed.ncbi.nlm.nih.gov/11918531/ . In in 41 (5.1%) of 803 autopsies showing invasive candidiasis in the USA, candidaemia was detected in 16 (43%) of all 37 cases with blood cultures (Berenguar, 1992) https://pubmed.ncbi.nlm.nih.gov/8243032/ . Among 94 haematological malignancy patients who underwent autopsy in Japan, blood culture sensitivity (at least one bottle positive) was 21.3% (Kami, 2022). A systematic review of the performance of *Candida* PCR compared with blood culture found blood cultures positive in 38% (29 to 46%) of patients with invasive candidiasis (Avni, 2011) https://pubmed.ncbi.nlm.nih.gov/21106797/ A diagnostic comparison study utilising beta 1,3-D-glucan and PCR detection found 38% of invasive and peritoneal candidiasis cases to have had positive blood cultures (Nguyen 2012) https://pubmed.ncbi.nlm.nih.gov/22431804/ . In patients receiving empirical antifungal therapy in Spain, 42 were found to have invasive candidiasis and only 4 (10%) had a positive blood culture for *Candida* (Martinez-Jimenez, 2015) https://pubmed.ncbi.nlm.nih.gov/25900160/ . In COVID-19 patients, PCR for *Candida* was positive in 7 of 85 (8.2%) compared to 1 out of 85 (1.2%) in blood culture (Seitz, 2023) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9241933/ . In Turkey, amongst 90 patients at high risk of candidiasis, a prospective evaluation of a PCR method found 18.9% positive, compared with 3.3% by blood culture (Bozok, 2021) https://pubmed.ncbi.nlm.nih.gov/34666656/ In children in Spain, PCR in blood was positive in 11.1% and blood culture in 3.2% (Candejas-Bueno, 2021) https://pubmed.ncbi.nlm.nih.gov/33044414/ Amongst 24 children in France with central nervous system candidiasis, blood culture was positive in 58% (Chaussade, 2021) https://pubmed.ncbi.nlm.nih.gov/32577733/ In patients in Spain diagnosed with intraabdominal candidiasis, *Candida* was grown in blood culture in 23.5% (Fortun, 2020) https://pubmed.ncbi.nlm.nih.gov/31811285/ . Here is is assumed that blood cultures are positive in only 40% of those with invasive candidiasis.

Mortality of invasive candidiasis Search: "invasive candidiasis" "Survival" and the same search repeated replacing survival with "mortality". The same figure for invasive candidiasis mortality is used as for *Candida* bloodstream infection – 35%. This is based on fewer data. In Spain overall mortality in surgical ICU was 25.9% (Maseda, 2016) https://pubmed.ncbi.nlm.nih.gov/26750771/ Intraabdominal candidiasis in the USA had a 100-day mortality of 28% (Vergidis, 2016) https://pubmed.ncbi.nlm.nih.gov/27123857/ . A large multi-centre study in France of *Candida* peritonitis found mortality in the ICU to be 38% (Montravers, 2011) https://pubmed.ncbi.nlm.nih.gov/20825438/ . In Germany, among 137 patients with *Candida* peritonitis, the 30-day and overall mortality was 40.9% and 49.6% (Dubler, 2017) https://pubmed.ncbi.nlm.nih.gov/28370502/ In a prospective treatment study of *Candida* peritonitis in France the day 28 mortality was 28.5% in those with confirmed *Candida* peritonitis (Montravers, 2017) https://pubmed.ncbi.nlm.nih.gov/27746395/ In 13 hospitals in Italy, Spain, Brazil, and Greece over 2011-2013, overall 30-day hospital mortality was 27% with 38.9% mortality in ICU patients (Bassetti, 2015) https://pubmed.ncbi.nlm.nih.gov/26077063/ . In *Candida* mediastinitis mortality was 41% (Hoffman, 2013) https://pubmed.ncbi.nlm.nih.gov/22924997/. In France, post-cardiac surgery *Candida* mediastinitis led to a 60% mortality (Harari, 2023) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9817255/ Another French study of *Candida* mediastinitis found a 60% mortality (Moyon, 2022) https://pubmed.ncbi.nlm.nih.gov/34662391/ *Candida* sternal infection (literature review) found 14.3% mortality (Arikan, 2019) https://pubmed.ncbi.nlm.nih.gov/30264627/ A comparison of elderly and younger patients with

Candida peritonitis in Greece found a 43.5% mortality compared with 20.9% in those younger (Dimopoulos, 2017) https://pubmed.ncbi.nlm.nih.gov/28492295/ Overall mortality of children with central nervous system candidiasis was 42% (Chaussade, 2021) https://pubmed.ncbi.nlm.nih.gov/32577733/

Attributable mortality of invasive candidiasis without a positive blood culture Search: "invasive candidiasis" AND "attributable mortality". No published estimates can be found. Therefore the same figure is assumed as for *Candida* bloodstream infection – 65%.

***Pneumocystis* pneumonia in AIDS in adults and children**. Search: "Pneumocystis" AND "incidence". HIV patients were separated from non-HIV patients. Incidence rates are highly variable depending primarily on the number of HIV-infected patients in a given country and the proportion of them well controlled with antiretroviral therapy (and presumably taking anti-*Pneumocystis* prophylaxis. Country annual incidence rates vary from 0.1/100,000 (ie Bangladesh, Hungary, Jordan, Oman) to as high as 40/100,000 (Cameroon), 51.6/100,000 (Kenya), 48.2 (Nigeria in 2014, before the revision of the total HIV prevalence), 61.8/100,000 (Malawi), 151/100,000 (Mozambique) (Appedix 2 and https://gaffi.org/media/country-fungal-disease-burdens/). In 84 countries where we have estimated the annual incidence, the number of cases was 376,638. This omits several moderate or high burden HIV countries, mostly in central and western Africa, most countries in SE Europe (only Greece, Romania and Azerbaijan have been estimated), the Baltic states and Finland, Myanmar, Cambodia and Papua New Guinea in SE Asia and Bolivia, Nicaragua, and San Salvador in the Americas, along with some other smaller countries. In some countries such as Canada (252 cases), Taiwan (1251 cases), the USA (9765 cases), UK (587 cases) and Uruguay (48 cases) no distinction is made between HIV- and non-HIV cases is made. We have therefore taken the annual incidence of PCP in AIDS to be 400,000.

Mortality of PCP. Search: "Pneumocystis" AND "Survival" and the same search repeated replacing survival with "mortality". HIV patients were separated from non-HIV patients. In developed nations, the mortality of PCP ranges from 0-15% (Elango, 2022; https://pubmed.ncbi.nlm.nih.gov/35270461/ , Pereira-Diaz, 2019 https://pubmed.ncbi.nlm.nih.gov/31637227/, Figueiredo 2019 https://pubmed.ncbi.nlm.nih.gov/31076291/ Ceron, 2014, https://pubmed.ncbi.nlm.nih.gov/25327195/ A systematic review of PCP in sub-Saharan Africa found an overall mortality of 18.8% (range 0-71%) based on 12 studies (Wasserman, 2016) https://pubmed.ncbi.nlm.nih.gov/27612639/ . Co-infection with other pathogens increased mortality. We have assumed an overall 15% mortality for treated PCP across the world.

Attributable mortality of PCP in AIDS. Search: "Pneumocystis" AND "attributable mortality". The primary cause of death in HIV-infected patients with PCP in AIDS is respiratory failure caused by PCP. Some patients have co-infections, especially TB, bacterial bronchitis and cytomegalovirus activation. We have assumed that 90% of deaths are directly attributable to PCP.

Incidence of PCP in non-HIV patients. Search: "Pneumocystis" AND "incidence". Non-HIV patients were separated from HIV patients. In a number of developed countries the incidence of PCP in non-HIV patients significant exceeds HIV – notably in most OECD36 countries. The ratio of non-HIV to HIIV is variable, and significantly affected by diagnostic approach and coding. In most European countries there are 1.5 to 18 times the number of non-HIV to HIV-related PCP cases, with this ratio depending primarily on the incidence of late stage HIV cases. The country incidence for multiple OECD countries varies from ~0.8-3/100,000 (Suppl. 2 and https://gaffi.org/media/country-fungal-disease-burdens/) and we have therefore used a figure of 2/100,000 population in OECD 36 countries, a total of 26,400. To this we have added estimates for India (32,691, 2.35/100,000), Indonesia (15,400, 5.75/100,000) and China (9,241, 0.64/100,000) a total of 83,732. This figure has been uplifted by an arbitrary 25% to account for the remainder of the world, not yet estimated, a grand total of 104,665.

PCP mortality in non-HIV patients Search: "Pneumocystis" AND "Survival" and the same search repeated replacing survival with "mortality". Non-HIV patients were separated from HIV patients. The mortality of PCP in non-HIV patients varies by underlying disease, from 8% to 58% at 1 month, and higher at 12 months (Ayling-Smith, 2023) https://pubmed.ncbi.nlm.nih.gov/37367596/ . It is higher in those with a higher fungal burden as measured by PCR (Gronsen, 2023) https://pubmed.ncbi.nlm.nih.gov/37339716/ and in those with co-infections, especially cytomegalovirus (Lecuyer, 2022) https://pubmed.ncbi.nlm.nih.gov/34604908/ Overall mortality in non-HIV patients was 58% (Ceron, 2014) https://pubmed.ncbi.nlm.nih.gov/25327195/ Among 1,204 non-HIV patients with PCP in Spain, the overall mortality was 25.5% (Pereira-Diaz, 2019) https://pubmed.ncbi.nlm.nih.gov/31637227/ In 54 non-HIV patients with PCP and several underlying conditions, the crude mortality was 37% (Figueiredo 2019) https://pubmed.ncbi.nlm.nih.gov/31076291/ In 26 patients with Hodgkins disease, two (8%) patients died (Barreto, 2020) https://pubmed.ncbi.nlm.nih.gov/32623928/ A nationwide databses in the USA yielded an in-hospital mortality of 16% (Kanj, 2021) https://pubmed.ncbi.nlm.nih.gov/33549258/ In France, in 133 patients with PCP unrelated to HIV infection, the crude 30-day and 1-year mortality rates were 24.1% and 56.4% (Assal, 2021) https://pubmed.ncbi.nlm.nih.gov/33886692/ . A nationwide study in Germany from 2014-2019 found a 32% crude mortality (Kolbrink, 2022) https://pubmed.ncbi.nlm.nih.gov/35814339/ In a small study from China, the crude mortality of PCP among HIV-negative patients was 30% (Zhang, 2023) https://pubmed.ncbi.nlm.nih.gov/36319918/ In South Korea, 49.1% of 113 patients with PCP died (Kang, 2023) https://pubmed.ncbi.nlm.nih.gov/37374118/ In Norway, the all-cause 30-day mortality in 170 patients was 18.2% (Gronsen, 2023) https://pubmed.ncbi.nlm.nih.gov/37339716/ Using a global research network database, of 8031 HIV-negative patients with PCP, the 30-day, 10-weeks and 1-year crude mortality was 37%, 38% and 51% respectively (Barahona, 2023) https://pubmed.ncbi.nlm.nih.gov/36938147/

Attributable mortality of PCP in non-HIV patients Search: "Pneumocystis" AND "attributable mortality". Non-HIV patients were separated from HIV-infected patients. In a comparison of HIV positive and negative patients with PCP in Chile, the overall mortality was 58% and the attributable mortality 33% (Ceron, 2014) https://pubmed.ncbi.nlm.nih.gov/25327195/ In 20 Japanese patients with solid tumours and PCP, overall and 30-day mortality attributable to PCP and were 40% and 30%, respectively (Takeda, 2023) https://pubmed.ncbi.nlm.nih.gov/34479519/ In Italy, 25% of 20 patients died, 100% attributable to PCP, although some had co-infections (Bozzi, 2022) https://pubmed.ncbi.nlm.nih.gov/35568363/ Kang found that 50 of 55 deaths were attributable to PCP (90.1%) (Kang, 2023) https://pubmed.ncbi.nlm.nih.gov/37374118/ We have assumed a 35% attributable mortality.

Cryptococcal meningitis in AIDS, including mortality. No additional searches were done. Annual incidence estimates of cryptococcal meningitis in AIDS are taken from Rajasingham (2022) https://pubmed.ncbi.nlm.nih.gov/36049486/ , including estimates for mortality. Mortality varies widely, depending on whether amphotericin B, flucytosine or fluconazole, or a combination are used. Other key factors affecting survival include control of raised intracranial pressure, initiation of antiretroviral therapy and treatment adherence. In high income countries mortality is typically 15-20%, in low resource countries using fluconazole only for treatment, mortality is 50-70% at 3-6 months. A meta-analysis of meningitis in routine care settings in Africa found a pooled short-term (in-hospital or 2-week) mortality of 44% (95% CI: 39% to 49%, 40 studies) (Tenforde, 2020) https://pubmed.ncbi.nlm.nih.gov/31957332/ In the same study, mortality at 10-12 weeks was 51% (95% CI: 43% to 60%, I^2 = 60%) and at 9-12 months was 63% (95% CI: 46% to 78%, I^2 = 79%).

Cryptococcal meningitis in non-HIV patients. Search: "cryptococcal meningitis", restricted to "human". Only series with both HIV patients and non-HIV patients were selected and the ratios documented. Cryptococcal meningitis occurs in non-immunocompromised patients and in non-HIV infected, but immunocompromised people, especially after transplantation, in those on long term corticosteroids and in adult onset immunodeficiency syndrome (anti-gamma interferon antibody). The relative proportion of cases depends in part on the frequency of AIDS-associated cryptococcal meningitis. Some published examples of estimates or documented cases are shown in the table below.

Table S1. Patient cohorts with both HIV-associated and non-HIV-associated cryptococcal meningitis described.

Country	AIDS (%)	Immunodeficiency (%)	No underlying disease (%)	Author, year
Senegal	95 (89.6%)		11 (10.4%)	Sow, 2013
South Africa	86 (98.9%)		1 (1.1%)	Hiegsen, 2017
Senegal	52 (90%)		5 (10%)	Ossibi, 2018
Mozambique	55 (90.2%)		6 (9.8%)	Nhantumbo, 2022
Mali	611 (87.5%)		87 (12.5%)	Doumbo, 2023
Thailand	2389 (86.9%)	251 (9.1%)	108 (3.9%)	Chayakulkeeree, 2017
South Korea	6 (13.6%)		38 (86.4%)	Huh, 2017
Malaysia	700 (81.2%)	108 (12.6%)	47 (5.5%)	Valayuthan, 2018
Taiwan	51 (21%)	144 (59.3%)	48 (19.8%)	Huang, 2019
China	13,086 (20%)	26,172 (40%)	26,249 (40%)	Zhou, 2021
Indonesia*	7540 (86.9%)	790 (9.1%)	340 (3.9%)	Wahyuningsih, 2021
India	9682 (85.6%)		1844 (14.4%)	Ray, 2022
Colombia	719 (85.6%)	54 (6.4%)	65 (7.8%)	Alvarez, 2018
Argentina	372 (86.1%)	60 (13.9%)		Riera, 2018
Brazil	6694 (98%)		138 (2%)	Giacomazzi, 2016
Brazil	89 (79.4%)	4 (3.6%)	19 (17.0%)	Damasceno, 2023
Israel	16 (66.7%)	8 (33.3%)		Ben-Ami, 2015
Turkey	14 (21.2%	29 (43.9%)	23 (34.8%)	Hilmioğlu-Polat, 2019

France	76 (58.0%)	23 (17.6%)	32 (24.4%)	Gangneux, 2016
Italy	30 (58.8%)	21 (41.2%)		Bassetti, 2017
Morocco	35 (87.5%)	3 (7.5%)	2 (5%)	Bandadi, 2019
Algeria	289 (80%)		72 (20%)	Aisssat, 2023

* modelled on Thailand

Attributable mortality of cryptococcal meningitis. Search: "cryptococcal meningitis" AND "Survival" and the same search repeated replacing survival with "mortality" and separately 'attributable mortality". HIV patients were separated from non-HIV patients. Most patients with cryptococcal meningitis and AIDS who die, die of the meningitis. In Thailand, among HIV-infected patients, the in-hospital, 90-day, and 1-year mortality rates were 24.1%, 32.4%, and 52.2%, respectively, of which 57.7%, 62.7% and 44.4% were attributed to cryptococcal meningitis (Chaiwarith, 2014) https://pubmed.ncbi.nlm.nih.gov/24974648/ The other causes of death were three patients died from extended-spectrum b-lactamase (ESBL) producing *Escherichia coli* septicaemia, two patients died from PCP, one patient each died from ESBL producing *E. coli* urinary tract infection (UTI), *Acinetobacter baumannii* UTI, and antibiotic associated enterocolitis. In 154 non-HIV patients with cryptococcal meningitis in China, overall 1-year mortality was 28.7% and cause-specific mortality was 19.6% (attributable 68.3%) (Zhu, 2010) https://pubmed.ncbi.nlm.nih.gov/20392150/. Therefore we have assumed an 80% attributable mortality, given the severity and frequency of this disease in Africa.

Disseminated histoplasmosis in AIDS. Search: "histoplasmosis" AND "incidence" AND "HIV" An estimate for the incidence of disseminated histoplasmosis in HIV patients for Latin America and the Caribbean used three percentages, 30%, 50% and 70% of those with low CD4 counts for 2012 HIV prevalence data. The highest figure is more in accord with recent data from Guatemala and the rate of enrolment into a randomised treatment study. We have therefore used an annual estimate of 15,657 for Latin America. Rayens (2022) https://pubmed.ncbi.nlm.nih.gov/35036461/ found 4880 hospital discharges in the USA, but not exclusively HV patients, and we have assumed 33% are HIV related, or 1627. Estimates from Asia included 5528 cases from China (Zhou, 2021), 1060 cases from Indonesia (Wahyuningsih, 2021) https://pubmed.ncbi.nlm.nih.gov/33971053/ , 175 cases in Malaysia (Velayuthan, 2018) https://pubmed.ncbi.nlm.nih.gov/29562712/ , 166 cases in Vietnam (Duong, 2023) https://pubmed.ncbi.nlm.nih.gov/36564981/ and 32 in Thailand (Chayakulkeeree, 2017) https://pubmed.ncbi.nlm.nih.gov/28161742/ . In none of these countries is there any *Histoplasma* antigen detection capability, which severely limits diagnosis. No estimates are available for Myanmar, Cambodia or Laos where histoplasmosis is hyperendemic in some areas. A literature survey of cases in Israel and Europe over 15 years found 114 published cases (8 per year) (Antinori, 2021) https://pubmed.ncbi.nlm.nih.gov/34198597/ . Emerging data from Africa indicates low rates in Tanzania in Eastern Africa (1.5% of new febrile HIV patients) (Lofgren, 2012) https://pubmed.ncbi.nlm.nih.gov/22742942/ , but higher rates in central and Western Africa. In 2 recent surveys, more histoplasmosis cases than cryptococcosis cases were found in HIV in Ghana (Ocansey, 2022) https://pubmed.ncbi.nlm.nih.gov/35854987/ and more than TB in some parts of Nigeria, but not others (Oladele, 2022) https://pubmed.ncbi.nlm.nih.gov/36286009/ . A conservative 60 cases was estimated in South Africa (Schwartz, 2019) https://pubmed.ncbi.nlm.nih.gov/29164168/ , consistent with substantial under-diagnosis (Mapengo, 2022) https://pubmed.ncbi.nlm.nih.gov/36170322/). In Togo, an estimated 330 cases (4.5/100,000) were estimated based on the data from Tanzania, 10% of the incidence of PCP (Dorkenoo, 2019) https://pubmed.ncbi.nlm.nih.gov/34596932/ . If this percentage is applied to all sub-Saharan African countries for which we have a PCP estimate, 23,380 cases of disseminated histoplasmosis would be diagnosable in AIDS. So a realistic minimum global annual incidence estimate of disseminated histoplasmosis is 47,633 cases, with likely at least double this number, based on the much higher sensitivity of *Histoplasma* antigen compared with other diagnostic methods and its general lack of availability. A 50% uplift of this figure was used as the median estimate (range 47,633 – 95,266).

Mortality of disseminated histoplasmosis in AIDS. Search: "histoplasmosis" AND "Survival" and the same search repeated replacing survival with "mortality". Untreated disseminated histoplasmosis in AIDS is universally fatal. Assuming standard approaches to diagnosis, and amphotericin B or itraconazole therapy a 20-30% mortality is usual (Medina, 2021; Pasqualotto, 2023). Overall mortality in 65 patients with pulmonary histoplasmosis in HIV patients, most with AIDS, was 22% in French Guiana, despite antifungal therapy (Bourne-Watrin, 2023) https://pubmed.ncbi.nlm.nih.gov/37839020/.

Attributable mortality of disseminated histoplasmosis in AIDS. Search: "Pneumocystis" AND "Survival" and the same search repeated replacing survival with "attributable mortality". No data on attributable mortality is published, but it is documented that dual and triple opportunistic infections are relatively frequent. Therefore we have assumed of those who die, 80% of deaths are attributable to histoplasmosis.

I**ncidence and mortality of talaromycosis**. Search: "marneffei" AND "incidence". HIV patients were separated from non-HIV patients. Talaromycosis originates from SE Asia, and primarily affects this with AIDS. A small number of patients acquire the infection in SE Asia and present in their home country after travel. The diagnosis can usually be made, but some patients have occult disease. Most cases of talaromycosis occur in late stage AIDS (~89.9%; Ning, 2020)[1]. A systematic review summarised publications to 2019 and found prevalence in those who are HIV infected by country Vietnam 6.4%, Thailand 3.9%, southern China 3.3%, north-eastern India 3.2% and 2.1% in Malaysia, with no data for Laos, Cambodia, Myanmar, Singapore, Indonesia, Philippines, Papua New Guinea or Bangladesh (Qin, 2020). https://pubmed.ncbi.nlm.nih.gov/32727383/ The precise denominator is missing because this infection tends to occur in those with advanced HIV infection. One abstract estimated the annual incidence and projected data forwards (Ning, 2020; Narayanasamy et al, 2021) https://pubmed.ncbi.nlm.nih.gov/34678201/ , but has yet to be fully published. We have taken their estimate of 17,300 annual cases and uplifted it by 10% to account for non-HIV infected patients.

Mortality of talaromycosis. Search: "marneffei" AND "Survival" and the same search repeated replacing survival with "mortality". Mortality rates vary substantially, primarily related to the speed of diagnosis and institution of optimal therapy. Narayanasamy (2021) found a range of mortality in different countries 6.5% to 33.3%. Ning et al estimated 4,900 annual deaths (28.3%), and we have used 28% and also assumed >95% mortality in untreated cases and that 80% of these deaths are attributable to talaromycosis (in the absence of data).

Mucormycosis incidence. Search: "mucormycosis" AND "incidence". We have conservatively estimated an annual incidence in all countries of 2 cases per million (13,000) except India and Sri Lanka at 14/100,000 (195,076 + 3094 = 198,170), a total of 211,170 (Bitar, 2012) https://pubmed.ncbi.nlm.nih.gov/23020929/ (Prakash, 2013), https://pubmed.ncbi.nlm.nih.gov/30901907/ (Kato, 2021) https://pubmed.ncbi.nlm.nih.gov/33480122/ (Shih, 2022) https://pubmed.ncbi.nlm.nih.gov/35713608/

Mucormycosis mortality. A systematic review, including 66% of cases described from Asia found a 25.7% treated mortality and 100% untreated mortality (Sigera, 2023)[2], manuscript submitted; abstract presented at TIMM Athens, October 2023). No additional searches were done.

Mucormycosis ratio of diagnosed and treated cases to missed cases. The vast majority of rhinocerebral mucormycosis cases are diagnosed as they are so clinically obvious. Pulmonary and disseminated mucormycosis is mossed and may also occur in association with other fungal infections, so there is a general publication bias in favour of rhinocerebral localisation. We have assumed that 80% of cases are diagnosed and treated, globally.

Attributable mortality of mucormycosis. Search: "mucormycosis" AND "attributable mortality". In a series of 12 burned patients with mucormycosis in the USA, the overall mortality was 92%; however, autopsy attributed mucormycosis mortality was 54.5% (6 of 11) but three patients didn't have an autopsy so were 'excluded' from the attributable death group (Mitchell, 2014) https://pubmed.ncbi.nlm.nih.gov/24881507/. A series of 20 patients in Lebanon, had a 60% mortality (12 of 20), of which 20% (4 of 20) (33.3% attributable) were attributable to mucormycosis, the remainder to unspecified septic shock or multiorgan failure (El Zain, 2018) https://pubmed.ncbi.nlm.nih.gov/30121719/ One series of children with acute fungal rhinosinusitis with leukaemia in Egypt reports an overall mortality of 35% (12 of 34) and fungal-attributable mortality of 20% (7of 34) (58% attributable), of which the majority of attributable deaths were due to mucormycosis, rather than IA (Eissa, 2022) https://pubmed.ncbi.nlm.nih.gov/35134980/ We have assumed a 70% attributable mortality.

Coccidioidomycosis incidence. Most cases of coccidioidomycosis occur in the USA and Mexico. The US Centres for Disease Control and Prevention (CDC) published the 2019 surveillance reports for coccidioidomycosis - 20,061 cases (Smith, 2022) https://pubmed.ncbi.nlm.nih.gov/36006889/ . Separately Rayens et al (2022), reported 2265 hospitalisations with coccidioidomycosis as the primary reason in 2018 out of a total of 8,990 hospitalisations for coccidioidomycosis. In Mexico, Corzo-Leon (2015) https://pubmed.ncbi.nlm.nih.gov/26449505/ estimated 8552 new cases of coccidioidomycosis, with at least 85 being disseminated cases, including meningitis. These data are indicative of a minimum of 28,613 cases, without including other endemic areas in Central and South America. Assuming another 5% of cases from other countries, the global total is likely to be about 30,043 cases.

Coccidioidomycosis mortality. Search: "coccidioidomycosis" AND "Survival" and the same search repeated replacing survival with "mortality". Rayens et al (2022), reported 70 deaths directly caused by coccidioidomycosis in 2018 of 365 mentioning this diagnosis as a cause of death. Among 11,045 patients admitted to hospital with coccidioidomycosis over 12 years in the USA to 2017, Rush et al, found 3.6% died, with 277 of 826 (33.5%) of those on mechanical ventilation. https://pubmed.ncbi.nlm.nih.gov/37008578/. Jones et al (2018) examined death certification in Arizona, USA over the 6 years to 2013 and found under-reporting coccidioidomycosis as a cause or contributory cause of death to be under-reported by 2- to 7-fold, and possibly more https://pubmed.ncbi.nlm.nih.gov/28595294/). From 1998–2008 death certification in the USA put mortality related to coccidioidomycosis at 0.59 per million. Extrapolation from this figure, with a 7x uplift to account for underreporting and a ratio between the incidence estimates for USA and Mexico results in an estimated death toll of (0.59x7x333.29 = 1376 (USA) plus (8552/20,061) x 1376 = 569 (Mexico) + 5% = 2042 deaths.

Attributable mortality of coccidioidomycosis Search: "coccidioidomycosis" AND "attributable mortality". The vast majority of deaths from coccidioidomycosis are directly attributable to the fungal disease; the exceptions are some HIV-positive and other immunocompromised patients, as small minority of cases. We have assumed a figure of 90%.

Fungal asthma prevalence Search (Pubmed and Google): "asthma" AND "prevalence" Assessment of 220 population-based studies from 88 countries found a global prevalence of current asthma in those aged 5-69 years to be 5.4% (95% CI = 3.2-9.0) translating into 357.4 million (95% CI = 213.0-590.8) cases (Song, 2022) https://pubmed.ncbi.nlm.nih.gov/35765786/ . This is higher than the Global Burden of Disease project global prevalence estimate of 262.41 million (Wang, 2023) https://pubmed.ncbi.nlm.nih.gov/37353829/ . Of these, Song et al, estimated that 157.69 million children (aged 5-14 years inclusive were affected, and therefore 199.71 million adults to age 69 are affected. The overall prevalence of current asthma symptoms in GAN Phase I was 9.1% for children, 11.0% for adolescents, and 6.6% for adults. http://globalasthmareport.org/burden/burden.php

Severe asthma is closely linked with increasing fungal allergy, primarily to airborne moulds and oral antifungal therapy is partially effective in reliving symptoms and improving asthma control. Definitions of severe vary, and alternative phraseology is often used including poorly-controlled asthma, brittle asthma, difficult asthma and recurrent asthma exacerbations. Making the broad assumption that 10% of asthma in adults is severe (and most consuming of healthcare resources), this computes to a global population of severe asthma of about 20 million. Children (< 15 years) have been ignored for the purposes of estimation, as the prevalence of severe or poorly controlled asthma in children, after optimising standard inhaler therapies remains poorly documented.

The proportion of severe asthmatics with fungal sensitisation has been studied in the UK, Japan and Uganda, with percentages of 66% (O'Driscoll, 2009), https://pubmed.ncbi.nlm.nih.gov/19689458/ 29% (Masaki, 2017) https://pubmed.ncbi.nlm.nih.gov/28801088/ and 33% (Wardlaw, 2020) https://pubmed.ncbi.nlm.nih.gov/32515118/ . In addition to these studies, the percentage of severe asthmatics with *Aspergillus fumigatus* sensitisation has been studied in the UK (47%) and Cleveland USA (38%) (Schwartz, 1978) https://pubmed.ncbi.nlm.nih.gov/350936/ , also in the UK (36% and 24%) (Menzies, 2011; https://pubmed.ncbi.nlm.nih.gov/21261660/ Mistry, 2021 https://pubmed.ncbi.nlm.nih.gov/34534722/), Egypt (52%) (Sabry, 2016), https://pubmed.ncbi.nlm.nih.gov/28502150/ Singapore (12%) (Goh, 2017) https://pubmed.ncbi.nlm.nih.gov/28461762/ , Iran (14%) (Hedayati, 2018) https://pubmed.ncbi.nlm.nih.gov/30815611/ , India (51% of asthmatics admitted to ICU) (Agarwal, 2010) https://pubmed.ncbi.nlm.nih.gov/19207831/, (70% of severe asthmatics had ABPA) (Bhankhur, 2019) https://pubmed.ncbi.nlm.nih.gov/30706871/ (45% in poorly controlled asthmatics) (Rajagopal, 2020) https://pubmed.ncbi.nlm.nih.gov/31888791/ (17% in children with persistent asthma) (Gupta, 2018) https://pubmed.ncbi.nlm.nih.gov/29110335/ (54%) (Shahul, 2020) https://www.jcdr.net/articles/PDF/13698/43385_CE[Ra1]_F(KM)_PF1(AJ_KM)_PN(SL).pdf and Uganda (42%) (Kwizera, 2021) https://pubmed.ncbi.nlm.nih.gov/33945622/. *Aspergillus fumigatus* sensitisation alone underestimates total fungal sensitisation in severe asthmatic people (21% and 18% lower in the UK and Japan (O'Driscoll, 2009; Masaki, 2017; Wardlaw, 2020)). We have therefore assumed that 40% of adults with severe asthma have fungal allergy (so called severe asthma with fungal sensitisation (SAFS)). This translates to a 4% global prevalence of SAFS in adults with asthma - 8 million people.

Allergic bronchopulmonary aspergillosis (ABPA) is a subset of allergic bronchopulmonary mycosis (ABPM). ABPA is less common than SAFS except in India. Multiple studies from Iran, China, Saudi Arabia, Uganda, South Africa found a prevalence of ABPA among new patients evaluated in secondary or tertiary care for asthma to be 2.5% prevalence, with a higher prevalence in New Zealand and lower in Ireland and probably the USA (Denning, 2013; https://pubmed.ncbi.nlm.nih.gov/23210682/, Ma, 2011; https://pubmed.ncbi.nlm.nih.gov/22333503/, Varmaghani, 2016; https://pubmed.ncbi.nlm.nih.gov/27090362/, Kwizera, 2021). However in India ABPA is more common, estimated at 5% (Ray 2022) https://pubmed.ncbi.nlm.nih.gov/36589484/ and supported by a community prevalence study in northern India of 5.7% (Soundappan, 2023)

https://pubmed.ncbi.nlm.nih.gov/36808646/. Here we use 2.5% for all countries except India, where have used 5%.

ABPA has been estimated in cystic fibrosis for the countries with highest numbers of cystic fibrosis patients (~11,000 cases, including children) (Armstead, 2014) https://pubmed.ncbi.nlm.nih.gov/24914809/.

Prevalence estimates of ABPM are less common and the clinical implications less well established – we have ignored this population in this estimate, even though it may be similar in size to ABPA (Kwizera, 2021; Asano, 2021) https://pubmed.ncbi.nlm.nih.gov/32920094/ . Some patients with ABPA and ABPM do not have asthma, but we have no good prevalence estimate for these patients. There is also an overlap between ABPA and SAFS, which in 3 studies (UK and Egypt) was 20-30% (Menzies, 2011; Sabry, 2016; Mistry, 2021), except in India where it was 77% (Shahul, 2020). Together these prevalence estimates are labelled fungal asthma. Our estimate of adults with fungal asthma is calculated as 200 million x 4% (SAFS) + 200 million - 40.4 million (India) x 2.5% (ABPA) + 1,198,000 (ABPA, India) = 11.69 million.

Fungal exposure in children can precipitate asthma, especially notable in mouldy, damp homes. However development of sensitisation to fungi is less well-studied. Cohort studies of severe, therapy resistant asthma in children include children diagnosed with SAFS, but it is difficult to extrapolate to the larger population of children with moderate or severe asthma. ABPA does occur in children, but is rare. So we have ignored children in our estimates, pending future data.

Fungal asthma deaths. Search (Pubmed and google): "asthma" AND "mortality". The GBD estimate of global deaths from asthma in childhood is 12,900 (Zhang, 2022) https://pubmed.ncbi.nlm.nih.gov/35252064/ from a total of 461,000 deaths from asthma (GBD, 2023) https://pubmed.ncbi.nlm.nih.gov/37229504/ . After a small peak in early childhood, asthma deaths decline in older children and really only start to climb as affected patients reach their 40's with peak deaths in the 70's and early 80's (detailed example from Canada: www.canada.ca/content/dam/phac-aspc/documents/services/publications/diseases-conditions/asthma-chronic-obstructive-pulmonary-disease-canada-2018/pub-eng.pdf). There are multiple associations between fungal allergy (sensitisation) and worse asthma, including major impact on hospitalisation for asthma, but the direct link between fungal asthma and asthma death has yet to be formally proven or quantified. As the detailed enquiry into deaths from asthma in the UK found (Why asthma still kills The National Review of Asthma Deaths (NRAD) Confidential Enquiry report (https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills (May 2014)) multiple factors contribute to deaths from asthma. For this reason, we have conservatively estimated only a 20% contribution of fungal asthma to the total deaths from asthma. Also the impact of antifungal therapy on preventing deaths from severe asthma has not been explored, so we have tentatively assumed a 60% benefit, as shown for antifungal therapy response for SAFS and other forms of asthma linked to fungal infection (Denning, 2023) https://pubmed.ncbi.nlm.nih.gov/37544851/ . As the risk period extends over years, we have assumed a 25 year time frame for mortality risk and potential benefit from antifungal therapy.

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