The global burden of HIV-associated cryptococcal infection in adults in 2020: a modelling analysis

Radha Rajasingham, Nelesh P Govender, Alexander Jordan, Angela Loyse, Amir Shroufi, David W Denning, David B Meya, Tom M Chiller, David R Boulware

Summary

Background Cryptococcal meningitis is the most common cause of meningitis in adults living with HIV in sub-Saharan Africa. The estimates of national, regional, and global burden of cryptococcal meningitis are essential to guide prevention strategies and determine needs for diagnostic tests and treatments. We present a 2020 estimate of the global burden of HIV-associated cryptococcal infection (antigenaemia), cryptococcal meningitis, and cryptococcal-associated deaths.

Methods We defined advanced HIV disease as adults with a CD4 count of less than 200 cells/μL, as this group is at highest risk for cryptococcosis. We used UNAIDS estimates (2019–20) and population-based HIV impact assessment surveys (2016–18) to estimate the number of adults with CD4 counts of less than 200 cells/μL at risk for cryptococcosis, by country and region. Secondly, we summarised cryptococcal antigenaemia prevalence in those with a CD4 count of less than 200 cells/μL by reviewing published literature. Thereafter, we calculated the number of cryptococcal antigen (CrAg)-positive people in each country and region by multiplying the number with advanced HIV disease at risk for cryptococcal infection by the cryptococcal antigenaemia prevalence of the respective country or region. We estimated progression from cryptococcal antigenaemia to meningitis or death based on estimates from the published literature.

Findings We estimated that there were 4·3 million (IQR 3·0–4·8) adults with HIV and CD4 counts of less than 200 cells/μL globally in 2020. We calculated a mean global cryptococcal antigenaemia prevalence of 4·4% (95% CI 1·6–7·4) among HIV-positive people with CD4 counts of less than 200 cells/μL, corresponding to 179 000 cases (IQR 133 000–219 000) of cryptococcal antigenaemia globally in 2020. Annually, we estimated that there are 152 000 cases (111 000–185 000) of cryptococcal meningitis, resulting in 112 000 cryptococcal-related deaths (79 000–134 000). Globally, cryptococcal disease accounts for 19% (13–24) of AIDS-related mortality.

Interpretation Despite a reduction in the estimated absolute global burden of HIV-associated cryptococcal meningitis compared with 2014, likely to be due to antiretroviral therapy expansion, cryptococcal disease still accounts for 19% of AIDS-related deaths, similar to 2014 estimates. To end cryptococcal meningitis deaths by 2030, cryptococcal diagnostics, meningitis treatments, and implementation of preventive screening are urgently needed.

Funding None.

Lancet Infect Dis 2022

Published **Online** August 29, 2022 https://doi.org/10.1016/S1473-3099(22)00499-6

See **Online/Comment** https://doi.org/10.1016/S1473-3099(22)00516-3

Division of Infectious Diseases and International Medicine, Department of Medicine, University of Minnesota, Minneapolis, MN, USA (R Rajasingham MD, D B Meya PhD, Prof D R Boulware MD); **National Institute for Communicable Diseases, National Health Laboratory Service and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa** (N P Govender MMed); **Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA** (A Jordan MPH, T M Chiller MD); **Centre for Global Health, Institute for Infection and Immunity, St George's University of London, London, UK** (A Loyse MD); **Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK** (Prof D W Denning MD); **Global Action Fund for Fungal Infections, Geneva, Switzerland** (Prof D W Denning); **Infectious Diseases Institute, Makerere University, Kampala, Uganda** (D B Meya); **CDC Foundation, Atlanta, GA, USA** (A Shroufi MPH)

Correspondence to: Dr Radha Rajasingham, Division of Infectious Diseases and International Medicine, Department of Medicine, University of Minnesota, Minneapolis, MN 55455, USA **radha@umn.edu**

For **UNAIDS estimates** see https://aidsinfo.unaids.org/

Introduction

Cryptococcal meningitis is the most common cause of meningitis in adults living with HIV in sub-Saharan Africa.[1] In 2014, an estimated 223 100 people developed cryptococcal meningitis globally, resulting in 181 100 deaths, which account for 15% of all AIDS-related deaths.[2] In 2020, UNAIDS estimated that 580 000 (range 400 000–850 000) AIDS-related deaths occurred among adults globally.

Cryptococcosis is unique among AIDS-related opportunistic infections in that cryptococcal antigen (CrAg) is detectable in the blood (antigenaemia) weeks to months before the onset of meningitis symptoms. Cryptococcal antigenaemia represents early disseminated infection, which is initially subclinical or minimally symptomatic. CrAg screening and pre-emptive treatment with fluconazole for those with cryptococcal antigenaemia, coupled with antiretroviral therapy (ART), reduces mortality in people with advanced HIV disease.[3,4] Despite clinical trial data confirming the survival benefit of CrAg screening and pre-emptive treatment,[4] only a few nations have adopted a national CrAg screening programme, with variable uptake from the population. However, other countries are also considering the cost–benefit trade-off of this screen-and-treat strategy.[5,6]

Estimates of the current incidence of cryptococcal disease are needed to quantify the diagnostic strategies, treatment commodities needed, and the potential lives saved with implementation of prevention and improved treatment strategies. Furthermore, new therapeutic strategies are being evaluated to reduce the high mortality associated with cryptococcal meningitis.[7] Since the last estimate of HIV infection prevalence of 223 100 cases of cryptococcal infection globally (using data from 2014),[2] global AIDS-related deaths among adults have decreased by an estimated 28%, from 800 000 deaths in 2014

Research in context

Evidence before this study

Cryptococcus neoformans is the most common cause of meningitis among adults in sub-Saharan Africa, due to the burden of HIV infection. We searched PubMed using the terms "cryptococcal meningitis" and "burden" on May 31, 2022, with no restrictions on language or date. Two studies have estimated the global burden of cryptococcal infection. One of the studies was published in 2008 and estimated the global incidence of cryptococcosis as 957 900 cases per year (range 371 700–1 544 000). This estimate was based on published cohorts primarily from the era before antiretroviral therapy became available, and the wide ranges indicate the high level of uncertainty of these estimates. The study used just three incidence publications to derive estimates for sub-Saharan Africa. The other study was published in 2017, and estimated the global burden of cryptococcal meningitis as 223 100 cases per year. This estimate used 2014 data from UNAIDS, and emerging country-specific data on cryptococcal antigen (CrAg) prevalence. Since the last estimate, AIDS-related deaths have declined by 28%. Antiretroviral therapy coverage has increased to 27·5 million adults (up from 15 million in 2014) and integrase inhibitors are now first-line therapy in many large HIV programmes.

Added value of this study

This is an updated global estimate of the burden of cryptococcal infection, using data from 2020. The landscape of HIV infection has changed drastically since the last estimate of global burden in 2014. We provide an updated estimate of the global incidence of HIV-associated cryptococcal disease using published UNAIDS data on HIV incidence, antiretroviral therapy access, retention in care, and published CrAg prevalence data.

Implications of all the available evidence

The estimates of national, regional, and global burden of cryptococcal meningitis are key to guide prevention strategies and determine needs for diagnostic tests, antifungal medicines, and medical supplies, such as diagnostics, lumbar puncture needles, and manometers. We estimate that cryptococcal disease still accounts for 19% of AIDS-related deaths, similar to 2014 estimates. To end cryptococcal meningitis deaths by 2030, cryptococcal diagnostics, meningitis treatments, and implementation of preventive screening are critically needed.

to 580 000 in 2020. By 2020, ART coverage had increased to 27·5 million adults, up from 15 million in 2014, and integrase inhibitors are now first-line therapy in many large HIV programmes.

In this Article, we present an updated estimate of the global burden of HIV-associated cryptococcal infection (antigenaemia), cryptococcal meningitis, and cryptococcal-associated deaths using 2020 data.

For **HIV impact assessment surveys from the International Center for AIDS Care and Treatment Program** see https://phia.icap.columbia.edu/resource_categories/final-reports/

Methods

Definition of advanced HIV disease

We defined advanced HIV disease as adults with a CD4 count of less than 200 cells/μL, as this group is at highest risk for cryptococcosis. WHO defines advanced HIV disease as a CD4 count of less than 200 cells/μL or those with WHO clinical stage 3 or 4 of HIV disease.[8] We used only CD4 estimates, as WHO clinical staging is frequently inaccurate when assessed by non-medical health-care workers, and therefore might not appropriately identify those severely immunosuppressed.[9] Although children younger than 5 years with HIV are considered to have advanced disease,[8] we did not consider children in this analysis as the risk of opportunistic infections such as cryptococcosis, along with screening and treatment recommendations, differ substantially from those for adults.[10]

Data sources

For estimates of the proportion with a CD4 count of less than 200 cells/μL, we used UNAIDS 2020 estimates[2] and population-based HIV impact assessment surveys from 2016 to 2018, conducted by the International Center for AIDS Care and Treatment Program and Centers for Diseases Control and Prevention in partnership with national HIV programmes.

UNAIDS publishes annual reports of the HIV pandemic by country and region. The most recent report was published in 2021 and uses data gathered in 2020. For our study, we used UNAIDS published estimates of the number of adults living with HIV and the proportion of people living with HIV who know their status to estimate the number of adults living with HIV who do not know their status. We used UNAIDS estimate of adults on ART to calculate the number of adults not on ART. Finally, we used the UNAIDS point estimates and range of uncertainty of the proportion with suppressed viral loads to calculate the proportion on ART with virological non-suppression (suppression defined as a viral load of <1000 copies/mL). If no country-level estimate was reported in the past 3 years for the proportion achieving viral suppression, we used the regional estimate. If no UNAIDS estimates were provided for the number of adults living with HIV in a country, this country was not included in our country-level analysis; however, such countries were included in regional estimates.

UNAIDS also publishes estimates of the proportion of people living with HIV with a late HIV diagnosis by country, defined as having an initial CD4 count of less than 200 cells/μL (appendix pp 4–5). A detailed

See Online for appendix

methodology on how UNAIDS estimates were obtained has been published elsewhere.[11] Where country-specific data were available, we used the 2020 estimate for the proportion with a CD4 count of less than 200 cells/μL at diagnosis of HIV. If unavailable for 2020, we used estimates from 2018 or 2019. For countries not reporting the proportion with a CD4 count of less than 200 cells/μL at time of HIV diagnosis between 2018 and 2020, we combined all available country-level estimates within the region (eg, southern and eastern Africa, or western and central Africa) and used the median and IQR for regional estimates. In summary, we used population-based HIV impact assessment estimates to estimate the proportion of people (1) not previously diagnosed with HIV with a CD4 count of less than 200 cells/μL, and (2) on ART with a CD4 count of less than 200 cells/μL. We used UNAIDS data to estimate the proportion newly entering HIV care (ART naive) with a CD4 count of less than 200 cells/μL.

Estimating the number with advanced HIV disease

As cryptococcal infection occurs in people with advanced immunosuppression, we first sought to generate estimates of the number of individuals with advanced HIV disease. For the purposes of this analysis, we assumed that the vast majority of people living with HIV with a CD4 count of less than 200 cells/μL fall into one of three categories: (1) those who do not know their HIV status, (2) those newly diagnosed with HIV infection, entering HIV care but not yet on ART, and (3) those on ART without virological suppression (figure 1; appendix p 1).

Summarising CrAg prevalence by country and region

We summarised the prevalence of cryptococcal antigenaemia among those with advanced HIV disease, whereby detectable CrAg in peripheral blood reflects disseminated systemic infection.[12] To summarise cryptococcal antigenaemia prevalence, we identified all published studies and conference abstracts from Jan 1, 1989, to Dec 31, 2021, by searching PubMed, using the terms "cryptococcal antigen" AND "HIV". We included studies from both outpatient and inpatient settings (appendix p 1).

CrAg prevalence among people with a CD4 count of less than 200 cells/μL was analysed by country, along with the associated 95% CIs, calculated using Fisher's exact test. Outpatient and inpatient CrAg prevalence studies were standardised (appendix p 2). For countries without cryptococcal antigenaemia prevalence data, we used the pooled, weighted regional mean estimate.

Estimating number of CrAg-positive people

We calculated the number of people with cryptococcal antigenaemia by country and region. Specifically, we calculated number of CrAg-positive individuals among people with: (1) advanced HIV disease with unknown HIV status, (2) advanced HIV disease but not receiving ART, and (3) advanced HIV disease without virological suppression (>1000 copies/mL). We multiplied the number of people within each of these groups by the CrAg prevalence for the respective country. The sum of these three groups was the total estimate for CrAg-positive people by country. We also present country-specific absolute numbers and numbers per 100 000 HIV infections (appendix p 13).

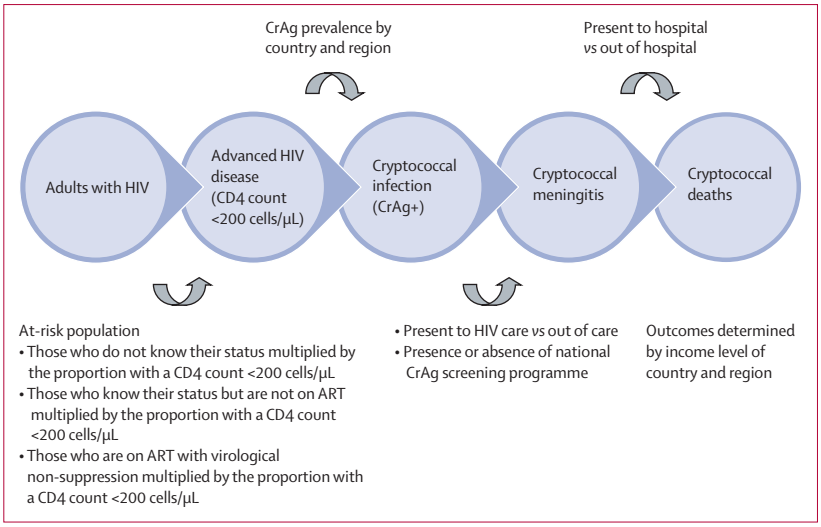

Figure 1: **Model structure**
The inputs are summarised in the appendix (pp 1–11). Arrows highlight the progression of people from one group to the next. Additional text below summarises further categorisation of each group. ART=antiretroviral therapy. CrAg=cryptococcal antigen.

Estimating the progression from antigenaemia to meningitis

The number of people progressing to cryptococcal meningitis was calculated considering the likelihood of a CrAg-positive person engaging in HIV care, receiving pre-emptive fluconazole through a CrAg screening programme, and receiving effective ART. We identified 35 studies from the published literature to calculate the weighted mean of progression from asymptomatic CrAg-positive infection to cryptococcal meningitis with fluconazole pre-emptive therapy. We identified 17 studies that summarised the prevalence of meningitis (subclinical or mildly symptomatic) at the time of CrAg screening. The weighted percentage of those with meningitis at the time of CrAg screening was 35%, and once these people were excluded, we estimated that an additional 11% would progress to develop meningitis during a 6-month period, despite pre-emptive fluconazole and ART (appendix p 8).

Progression from asymptomatic CrAg-positive infection to cryptococcal meningitis without pre-emptive fluconazole is no longer ethical to study in clinical trials, although there is evidence that nearly 67% (95% CI 46–84) of people with a CD4 count of less than 100 cells/μL progress to meningitis or death without fluconazole (despite ART).[3,13,14] Despite the recommendation for lumbar puncture and cerebrospinal fluid testing for asymptomatic CrAg-positive people by some national guidelines, frequently this

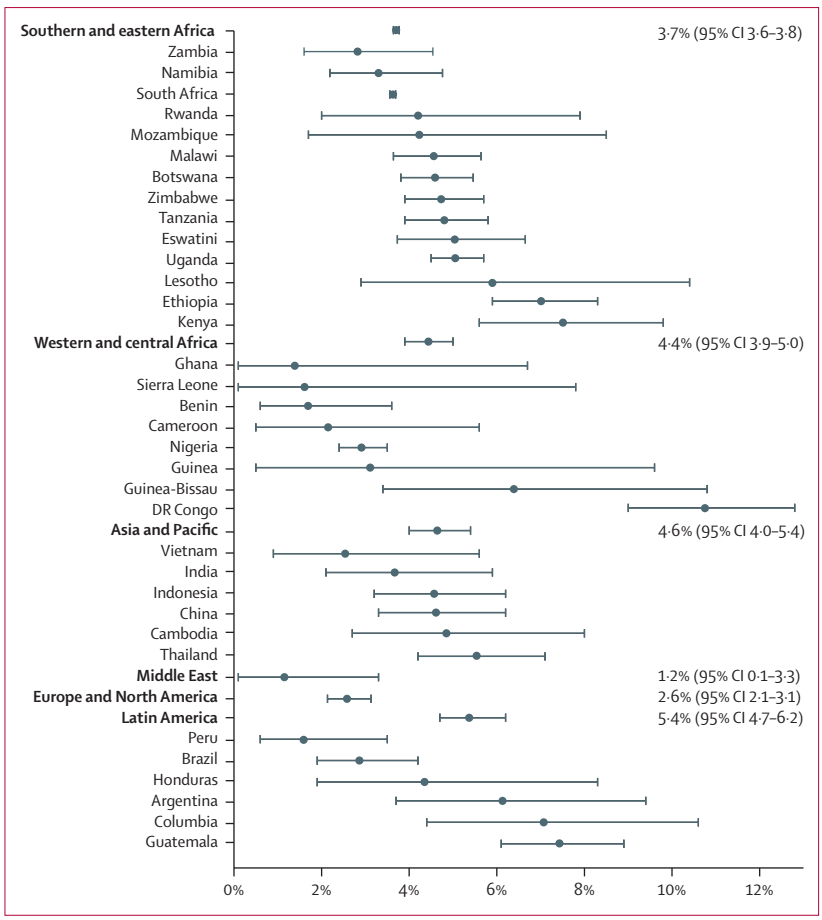

Figure 2: **CrAg prevalence by country among people living with HIV with a CD4 count of less than 200 cells/μL**
There were no data available for the Caribbean region or North Africa. CrAg prevalence for the Caribbean region were extrapolated from Latin American estimates. Similarly, data for the North African region were extrapolated from estimates from the Middle East. CrAg=cryptococcal antigen/antigenaemia.

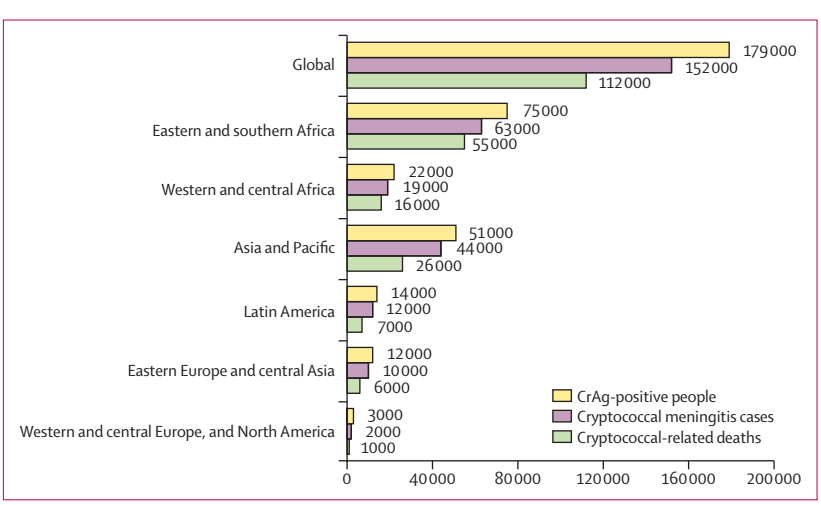

Figure 3: **Global and regional estimates of the incidence of cryptococcal antigenaemia, cryptococcal meningitis, and cryptococcal-related deaths**
The Caribbean, the Middle East, and North Africa are not shown here due to the very low incidences. CrAg=cryptococcal antigen.

strategy is difficult to implement in resource-limited settings due to the scarcity of lumbar puncture capability, and patient refusal especially if asymptomatic. Without access to either pre-emptive fluconazole or ART, we presumed 95% of CrAg-positive people would progress to meningitis or death.[3,14]

Estimating the progression from cryptococcal meningitis to death

Mortality estimates include death from HIV-associated cryptococcal meningitis and other causes of death among CrAg-positive people. 1-year mortality after cryptococcal meningitis is summarised in the appendix (p 11). Mortality among people who have been hospitalised has been estimated previously.[15] However, these estimates do not include people who do not present to the hospital or present late to hospital.

We stratified those who present to hospital for meningitis care based on underlying HIV status (appendix pp 10–11). We assumed that those who do not know their HIV status and have meningitis might be less likely to access medical care compared with a person on ART with virological failure who has previously attended outpatient HIV clinics.

Finally, we estimated that about 10% of CrAg-positive people without cryptococcal meningitis die of other concomitant conditions, not necessarily of cryptococcosis (appendix p 8). Potential alternative causes of death include tuberculosis, histoplasmosis, malnutrition or wasting, sepsis, other opportunistic infections, or cancer.

See the appendix (pp 1–3) for the methodology regarding estimates of cryptococcal-related deaths as a proportion of AIDS-related deaths, calculations related to benefit of the CrAg screening programme, and estimates of uncertainty to generate IQRs. No ethical review was sought for this study as there were no participants. We adhered to the STROBE guidelines for reporting observational studies.[16] All modelling, and calculations were done using Microsoft Excel 2016.

Role of the funding source

There was no funding source for this study.

Results

In 2020, UNAIDS estimated that 36·7 million adults (range 28·9–43·2) worldwide were living with HIV, of which 23·8 million (19·5–28·5) reside in sub-Saharan Africa. Globally, 27·5 million (range 16·2–38·0) adults were receiving ART. We estimated that 4·3 million (IQR 3·0–4·8) adults globally had advanced HIV disease (defined as CD4<200 cells/μL and corresponding to 12% of people living with HIV [range 10–15]), of whom 2·5 million (58%) live in sub-Saharan Africa.

We identified 53 CrAg prevalence studies from sub-Saharan Africa, ten from Asia, ten from Latin America, two from Europe, two from the Middle East, and one from North America (figure 1). We calculated the

	CrAg-positive	Cryptococcal meningitis	Cryptococcal deaths*	Proportion of AIDS-related deaths
Global	179 000 (133 000–219 000)	152 000 (111 000–185 000)	112 000 (79 000–134 000)	19% (13–24)
Eastern and southern Africa	75 000 (55 000–95 000)	63 000 (45 000–80 000)	55 000 (39 000–70 000)	21% (15–28)
Western and central Africa	22 000 (19 000–26 000)	19 000 (16 000–22 000)	16 000 (13 000–19 000)	15% (12–18)
Asia and Pacific	51 000 (42 000–60 000)	44 000 (35 000–51 000)	26 000 (21 000–30 000)	20% (13–22)
Latin America	14 000 (10 000–17 000)	12 000 (9000–14 000)	7000 (5000–9000)	23% (16–30)
Eastern Europe and central Asia	12 000 (11 000–13 000)	10 000 (9000–11 000)	6000 (5000–7000)	19% (17–22)
Western central Europe and North America	3000 (2000–4000)	2000 (1500–3000)	1000 (700–1400)	8% (5–11)
Caribbean	2000 (1700–2300)	1700 (1400–1900)	1000 (800–1100)	19% (15–23)
Middle East and North Africa	500 (100–600)	400 (100–500)	200 (100–300)	3% (1–5)

Data are raw data from the model output (IQR). CrAg=cryptococcal antigen. *Cryptococcal deaths include deaths among those with diagnosed meningitis as well as deaths in CrAg-positive people without overt meningitis. Sub-Saharan Africa consists of total estimates of Eastern and Southern Africa and Western and Central Africa.

Table: **Regional estimates of the burden of cryptococcosis in 2020**

mean global cryptococcal antigenaemia prevalence of 4·4% (95% CI 1·6–7·4) among people with CD4 counts of less than 200 cells/μL, corresponding to 179 000 (IQR 133 000–219 000) cases of cryptococcal antigenaemia globally per year (figure 2). Of these 179 000 individuals, we estimated that 101 000 (56% [IQR 40–66]) were people who were not yet on ART, 37 000 (21% [20–23]) were people with virological failure, and 42 000 (22% [21–23]) were unaware of their HIV infection. Annually, we estimated that there are 152 000 (IQR 111 000–185 000) cases of cryptococcal meningitis, resulting in 112 000 cryptococcal-related deaths (IQR 79 000–134 000; figure 3; table). In sub-Saharan Africa (combining southern and eastern with western and central African regions), where historically the burden of cryptococcal infection has been the greatest, an estimated 97 000 adults (IQR 73 000–120 000) had cryptococcal antigenaemia in 2020, 82 000 adults (61 000–101 000) developed cryptococcal meningitis, and 71 000 (52 000–88 000) cryptococcal-related deaths occurred (accounting for 63% of all cryptococcal-related deaths; figure 4). The region with the second highest incidence of cryptococcal meningitis is Asia and Pacific, with 44 000 (IQR 35 000–51 000) cryptococcal meningitis cases and 26 000 (21 000–30 000) cryptococcal-related deaths annually (figure 3). The appendix (p 13) summarises cryptococcal infection per 100 000 HIV infections in select countries. Globally, cryptococcal disease resulted in 112 000 (19% [IQR 13–24]) of 580 000 AIDS-related deaths in 2020.

If all regions implemented national CrAg screening programmes, where at least 80% of people entering or re-entering HIV care were screened and received fluconazole pre-emptive therapy, we estimate that 34 000 cases of cryptococcal meningitis could be avoided annually (22% of the current meningitis cases). With implementation of CrAg screening programmes globally to identify CrAg-positive people before onset of meningitis, 21 000 lives could be saved annually (19% of current cryptococcal-related deaths). With wider implementation of lumbar punctures to identify early meningitis among CrAg-positive people, especially those who are symptomatic or with high CrAg titres, more deaths could be averted. Sub-Saharan African and the Asia and Pacific regions have the highest proportion of cases of cryptococcal infection, and thus would experience the greatest reduction in mortality with implementation of CrAg screening programmes.

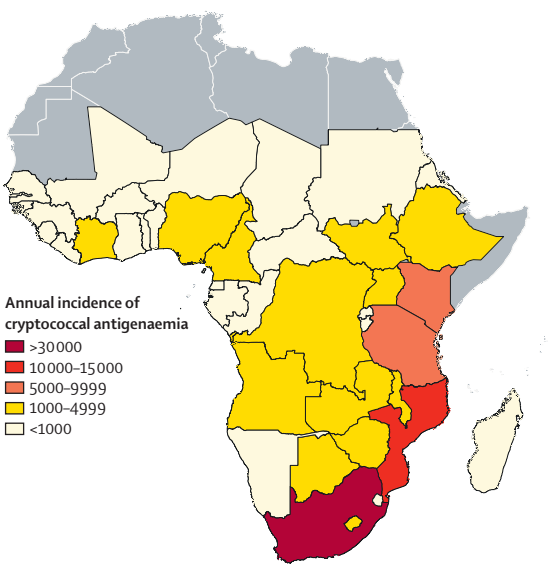

Figure 4: **Annual incidence of cryptococcal antigenemia in sub-Saharan Africa**
Top 10 countries, in terms of incidence of cryptococcal antigenaemia are South Africa, Mozambique, Kenya, DR Congo, Tanzania, Zambia, Nigeria, Malawi, Zimbabwe, and Ethiopia (appendix p 12).

Discussion

Although there has been a reduction in the estimated absolute global burden of HIV-associated cryptococcal meningitis since 2014, probably due to ART expansion and, to some degree, CrAg screening programmes,

cryptococcosis still results in 19% of AIDS-related deaths; the latter is largely unchanged from previous estimates in 2014. The persistent burden of infection suggests that death from cryptococcal infection remains a marker for failure in the HIV cascade of care. People at risk of cryptococcal infection have advanced HIV disease, either because they do not know their HIV status, have not engaged in outpatient HIV care and initiated ART, are on a failing ART regimen, or have had interruptions in treatment. Indeed, most people presenting with cryptococcal meningitis are now ART-experienced.[17]

UNAIDS estimates that 73% of people living with HIV globally are receiving ART, but only 61% of people living with HIV have suppressed viral loads. Contributing to the high continued prevalence of cryptococcosis are three key gaps in the HIV care cascade: (1) 27% of people living with HIV are not receiving ART, (2) 39% of people living with HIV do not have suppressed viral loads, and (3) 30% (IQR 24–41) of people living with HIV present for the first time with an initial a CD4 count of less than 200 cells/μL. Earlier identification and engagement in HIV care of people living with HIV would reduce the proportion presenting late to care, and would therefore reduce the number at risk for opportunistic infections. In conjunction with rapid ART initiation, identification of advanced HIV disease and appropriate screening for opportunistic infections, including cryptococcal infection, are essential. Enhanced active monitoring for virological failure and evidence-based interventions to improve adherence to care would increase the proportion with virological suppression and reduce the population at risk of opportunistic infections. Novel strategies to reduce ART interruption and improve treatment adherence, such as long-acting injectable ART, would probably reduce the burden of opportunistic infections. Furthermore, more implementation science programmes to address non-adherence to ART and optimise ART adherence are warranted.

Cryptococcal antigen detection using lateral flow devices approved by the US Food and Drug Administration are perhaps the ultimate test in microbiology—highly accurate, quick, easy to read, and inexpensive.[18] Diagnosis of antigenaemia before the onset of meningitis is optimal. Initiation of ART without diagnosing cryptococcal infection carries a considerable risk of death.[3,19] Greater access to CD4 testing to identify advanced HIV disease, followed by CrAg testing if advanced HIV disease is identified, is required to assist with expeditious diagnosis and access to effective pre-emptive therapy, together with health system strengthening interventions centred on improving ART adherence and early identification of ART failure. There are currently many limitations to the early diagnosis of cryptococcal meningitis, primarily related to access to CD4 testing, timely receipt of results, and availability of CrAg lateral flow assays and fluconazole.

To reduce cryptococcal-related deaths, global scale-up and investment into CrAg screening programmes along with adequate supply of pre-emptive treatment can ultimately prevent meningitis and thereby deaths, while potentially reducing long-term costs. Thus, testing is a start but rapid linkage to pre-emptive therapy following laboratory testing is necessary.[20] In South Africa, where reflexive laboratory CrAg screening of all CD4 samples less than 100 cells/μL is implemented on a national scale, only about 50% of CrAg-positive people receive fluconazole treatment (Govender NP, unpublished data). Unfortunately, national-level interventions and implementation strategies to retain people with advanced HIV disease in care, screen for opportunistic infections, and rapidly initiate ART are lacking in many countries and districts. Increased coverage of CrAg screening programmes would reduce cryptococcal deaths.

Therapeutics for cryptococcal meningitis remain inaccessible in many resource-limited settings, where the burden is greatest, because therapeutics are not locally manufactured. The preferred induction regimen (according to WHO) for adults with HIV-associated cryptococcal meningitis is amphotericin B and flucytosine for 7 days, followed by 7 days of high-dose fluconazole.[21] Most recently, a randomised controlled trial showed that single-dose liposomal amphotericin B with flucytosine and fluconazole is non-inferior to the WHO-recommended regimen, with significantly reduced side effects.[7] Unfortunately, flucytosine is generally unavailable in sub-Saharan Africa, Asia, and Latin America, although efforts are underway to improve access.[22,23] Without flucytosine regimens available, there is increased mortality, with the typical course for cryptococcal meningitis treatment being 14 days of amphotericin B with fluconazole; where amphotericin is unavailable or cannot be safely administered, suboptimal fluconazole monotherapy prevails.[21] Amphotericin B deoxycholate is notorious for medication-related side-effects, including rigors, fevers, chills, life-threatening hypokalaemia, and kidney injury. Manometers, which are considered the standard of care to measure and control intracranial pressure in cryptococcal meningitis to improve outcomes,[24] are likewise unavailable in most resource-limited settings. Finally, training of health-care workers in meningitis care and point-of-care diagnostic algorithms are needed to improve meningitis diagnosis in routine settings.[25] Clinical trials are underway to investigate new treatments and new implementation strategies to improve meningitis care in resource-poor settings. An initiative entitled *Ending HIV-associated CM deaths by 2030* has been announced recently, which lays out a comprehensive framework to address cryptococcal-related meningitis deaths, including targets and interventions for countries to minimise meningitis deaths.[26]

The primary limitation of our estimate is the quality of data inputs. We used UNAIDS published estimates on

the current state of HIV care globally.[11] These estimates sometimes had no confidence intervals and might not reflect the variation within a country or region. Countries without UNAIDS estimates for the number of people living with HIV were excluded from country-level analyses but included in regional estimates. The COVID-19 pandemic probably affected 2020 HIV estimates, although there is probably a high degree of variability on the impact of COVID-19 on HIV infection. Our unpublished data suggest that lockdowns resulted in fewer visits to HIV clinics and increased late presentation to care with advanced HIV disease. As a result, the numbers derived from UNAIDS might under-represent the true number with HIV infection, not on ART, or with virological failure, or both. Our assessment of the burden of cryptococcal infection, meningitis, and associated deaths could be underestimated given fewer people living with HIV presenting to care due to the COVID-19 pandemic and a greater proportion at risk of cryptococcal infection.

Our estimates might underestimate the burden of cryptococcal infection, as UNAIDS estimates of HIV infection are considerably lower than estimates from 2019 Global Burden of Disease data.[27] Specifically, UNAIDS estimates 680 000 AIDS-related deaths, whereas the Global Burden of Diseases data estimates 864 000 HIV-related deaths. If the latter is more accurate, then the burden of cryptococcal infection could be 20% higher than we estimate.

There are many unknowns regarding people with advanced HIV disease. Specifically, it is unknown what proportion of people living with HIV with virological non-suppression have advanced HIV disease or asymptomatic cryptococcal antigenaemia,[28] especially outside of sub-Saharan Africa. It is unknown (and challenging to study) what proportion of people living with HIV who do not know their HIV status have advanced HIV disease. CrAg prevalence studies in high-income and middle-income regions, including North America, Europe, and the Middle East, are needed to further understand the burden of meningitis and the value of CrAg screening. It is unknown what proportion of people with cryptococcal antigenaemia develop meningitis or die at home, without presenting to a hospital.[29,30] Among those few countries with CrAg screening programmes in place, detailed outcome data related to the proportion screened, proportion treated, and incidence of cryptococcal meningitis and death would be valuable metrics for stakeholders in other countries considering their own programmes. Timely results are crucial for identifying meningitis as early as possible, or even before it occurs in those who are CrAg-positive.

Finally, our estimates exclude children, where the burden of cryptococcal infection is lower, and people with non-HIV-associated cryptococcal infection. In South Africa, 2% of cryptococcal meningitis occurs in those younger than 18 years.[10] Pregnant and breastfeeding women are frequently excluded from cryptococcal studies and research in general, thus our estimates might underestimate the total burden of HIV-associated cryptococcal infection. A recent study on minimally invasive autopsies identified cryptococcosis as a leading cause of maternal death.[31]

With the expansion of HIV therapy, the absolute number of cryptococcal infections, cryptococcal meningitis, and cryptococcal-related deaths has declined, yet we estimate that cryptococcosis still accounts for 19% of AIDS-related deaths, which is unchanged from the estimate made in 2014.[2] However, in the past decade since CrAg screening was first recommended by WHO,[32] there has been some progress in implementation of cryptococcal prevention, which is generally cost-effective across low-income, middle-income, and high-income settings.[5,33] Implementation of the new framework to end cryptococcal-related meningitis deaths by 2030 is critically needed.[22] Specifically, to end cryptococcal-related meningitis deaths by 2030, the following steps are needed: (1) increased availability of diagnostics, (2) implementation of CrAg screening in people with advanced HIV, and (3) access and implementation of WHO-recommended optimised treatment regimens for cryptococcal meningitis, along with strengthening the HIV cascade of care and retention in ART programmes.

Contributors

RR performed the literature search, study design, data collection, data analysis, data interpretation, and writing of the original draft of the manuscript. RR and DRB directly accessed and verified the underlying data reported in the manuscript. NPG, AJ, AL, AS, DWD, DBM, and TMC contributed to the literature search, data analysis, data interpretation, and reviewing and editing the manuscript. DRB contributed to study design, data analysis, data interpretation, and reviewing and editing the manuscript. All authors read and approved the final version of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing

Raw data tables and individual country information will be made available with publication; please email the corresponding author to make such a request.

Declaration of interests

We declare no competing interests.

Acknowledgments

RR, DRB, and NPG are supported by the National Institute of Allergy and Infectious Diseases (K23AI138851, R01AI118511, U01AI125003). AL is in receipt of grants from EDCTP and ANRS outside the scope of this work. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Centers for Disease Control and Prevention.

References

1 Ellis J, Bangdiwala AS, Cresswell FV, et al. The changing epidemiology of HIV-associated adult meningitis, Uganda 2015–2017. *Open Forum Infect Dis* 2019; **6:** ofz419.

2 Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *Lancet Infect Dis* 2017; **17:** 873–81.

3 Meya DB, Manabe YC, Castelnuovo B, et al. Cost-effectiveness of serum cryptococcal antigen screening to prevent deaths among HIV-infected persons with a CD4+ cell count < or = 100 cells/microL who start HIV therapy in resource-limited settings. *Clin Infect Dis* 2010; **51:** 448–55.

4 Mfinanga S, Chanda D, Kivuyo SL, et al. Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial. *Lancet* 2015; **385:** 2173–82.

5 Rajasingham R, Meya DB, Greene GS, et al. Evaluation of a national cryptococcal antigen screening program for HIV-infected patients in Uganda: a cost-effectiveness modeling analysis. *PLoS One* 2019; **14:** e0210105.

6 Rajasingham R, Meya DB, Boulware DR. Integrating cryptococcal antigen screening and pre-emptive treatment into routine HIV care. *J Acquir Immune Defic Syndr (1999)* 2012; **59:** e85–91.

7 Jarvis JN, Lawrence DS, Meya DB, et al. Single-dose liposomal amphotericin B treatment for cryptococcal meningitis. *N Engl J Med* 2022; **386:** 1109–20.

8 WHO. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. July 1, 2017. https://www.who.int/publications/i/item/9789241550062 (accessed June 1, 2022).

9 Hakim J, Musiime V, Szubert AJ, et al. Enhanced prophylaxis plus antiretroviral therapy for advanced HIV infection in Africa. *N Engl J Med* 2017; **377:** 233–45.

10 National Institute for Communicable Diseases. GERMS-SA Annual Report 2019. 2019. https://www.nicd.ac.za/wp-content/uploads/2021/02/GERMS-Annual-Review-2019_.pdf (accessed Nov 15, 2021).

11 UNAIDS. Global AIDS monitoring 2022. 2022. https://www.unaids.org/sites/default/files/media_asset/global-aids-monitoring_en.pdf (accessed March 22, 2021).

12 Rajasingham R, Wake RM, Beyene T, Katende A, Letang E, Boulware DR. Cryptococcal meningitis diagnostics and screening in the era of point-of-care laboratory testing. *J Clin Microbiol* 2019; **57:** e01238–18.

13 Longley N, Jarvis JN, Meintjes G, et al. Cryptococcal antigen screening in patients initiating ART in South Africa: a prospective cohort study. *Clin Infect Dis* 2016; **62:** 581–87.

14 Letang E, Müller MC, Ntamatungiro AJ, et al. Cryptococcal antigenemia in immunocompromised human immunodeficiency virus patients in rural Tanzania: a preventable cause of early mortality. *Open Forum Infect Dis* 2015; **2:** ofv046.

15 Rajasingham R, Rolfes MA, Birkenkamp KE, Meya DB, Boulware DR. Cryptococcal meningitis treatment strategies in resource-limited settings: a cost-effectiveness analysis. *PLoS Med* 2012; **9:** e1001316.

16 UK EQUATOR Centre. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. April 7, 2022. https://www.equator-network.org/reporting-guidelines/strobe/ (accessed June 7, 2022).

17 Flynn AG, Meya DB, Hullsiek KH, et al. Evolving failures in the delivery of human immunodeficiency virus care: lessons from a Ugandan meningitis cohort 2006–2016. *Open Forum Infect Dis* 2017; **4:** ofx077.

18 Tadeo KK, Nimwesiga A, Kwizera R, et al. Evaluation of the diagnostic performance of a semiquantitative cryptococcal antigen point-of-care assay among HIV-infected persons with cryptococcal meningitis. *J Clin Microbiol* 2021; **59:** e0086021.

19 Rhein J, Hullsiek KH, Evans EE, et al. Detrimental outcomes of unmasking cryptococcal meningitis with recent ART initiation. *Open Forum Infect Dis* 2018; **5:** ofy122.

20 Medina N, Alastruey-Izquierdo A, Bonilla O, et al. A rapid screening program for histoplasmosis, tuberculosis, and cryptococcosis reduces mortality in HIV patients from Guatemala. *J Fungi (Basel)* 2021; **7:** 268.

21 WHO. Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. March 1, 2018. https://www.who.int/publications/i/item/9789241550277 (accessed March 14, 2022).

22 Shroufi A, Chiller T, Jordan A, et al. Ending deaths from HIV-related cryptococcal meningitis by 2030. *Lancet Infect Dis* 2021; **21:** 16–18.

23 UNITAID. Nine quick facts about Unitaid's investment in advanced HIV. Jan 24, 2019. https://unitaid.org/news-blog/targeting-opportunistic-infections-to-cut-hiv-related-deaths/#en (accessed Aug 26, 2021).

24 Rolfes MA, Hullsiek KH, Rhein J, et al. The effect of therapeutic lumbar punctures on acute mortality from cryptococcal meningitis. *Clin Infect Dis* 2014; **59:** 1607–14.

25 Oladele RO, Jordan A, Akande P, et al. Tackling cryptococcal meningitis in Nigeria, one-step at a time; the impact of training. *PLoS One* 2020; **15:** e0235577.

26 Ending cryptoocccal meningitis deaths by 2030: strategic framework. May 13, 2021. https://msfaccess.org/ending-cryptococcal-meningitis-deaths-2030-strategic-framework (accessed Feb 1, 2022).

27 Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; **396:** 1204–22.

28 Mpoza E, Rajasingham R, Tugume L, et al. Cryptococcal antigenemia in human immunodeficiency virus antiretroviral therapy-experienced Ugandans with virologic failure. *Clin Infect Dis* 2020; **71:** 1726–31.

29 French N, Gray K, Watera C, et al. Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. *AIDS* 2002; **16:** 1031–38.

30 Liechty CA, Solberg P, Were W, et al. Asymptomatic serum cryptococcal antigenemia and early mortality during antiretroviral therapy in rural Uganda. *Trop Med Int Health* 2007; **12:** 929–35.

31 Letang E, Rakislova N, Martinez MJ, et al. Minimally invasive tissue sampling: a tool to guide efforts to reduce AIDS-related mortality in resource-limited settings. *Clin Infect Dis* 2021; **73** (suppl 5)**:** S343–50.

32 WHO. Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. December, 2011. https://apps.who.int/iris/handle/10665/44786 (accessed May 2, 2022).

33 Rajasingham R, Boulware DR. Reconsidering cryptococcal antigen screening in the U.S. among persons with CD4 <100 cells/mcL. *Clin Infect Dis* 2012; **55:** 1742–44.