Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis

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Summary

Background **Cryptococcus is the most common cause of meningitis in adults living with HIV in sub-Saharan Africa. Global burden estimates are crucial to guide prevention strategies and to determine treatment needs, and we aimed to provide an updated estimate of global incidence of HIV-associated cryptococcal disease.**

Methods **We used 2014 Joint UN Programme on HIV and AIDS estimates of adults (aged >15 years) with HIV and antiretroviral therapy (ART) coverage. Estimates of CD4 less than 100 cells per μL, virological failure incidence, and loss to follow-up were from published multinational cohorts in low-income and middle-income countries. We calculated those at risk for cryptococcal infection, specifically those with CD4 less than 100 cells/μL not on ART, and those with CD4 less than 100 cells per μL on ART but lost to follow-up or with virological failure. Cryptococcal antigenaemia prevalence by country was derived from 46 studies globally. Based on cryptococcal antigenaemia prevalence in each country and region, we estimated the annual numbers of people who are developing and dying from cryptococcal meningitis.**

Findings **We estimated an average global cryptococcal antigenaemia prevalence of 6·0% (95% CI 5·8–6·2) among people with a CD4 cell count of less than 100 cells per μL, with 278 000 (95% CI 195 500–340 600) people positive for cryptococcal antigen globally and 223 100 (95% CI 150 600–282 400) incident cases of cryptococcal meningitis globally in 2014. Sub-Saharan Africa accounted for 73% of the estimated cryptococcal meningitis cases in 2014 (162 500 cases [95% CI 113 600–193 900]). Annual global deaths from cryptococcal meningitis were estimated at 181 100 (95% CI 119 400–234 300), with 135 900 (75%; [95% CI 93 900–163 900]) deaths in sub-Saharan Africa. Globally, cryptococcal meningitis was responsible for 15% of AIDS-related deaths (95% CI 10–19).**

Interpretation **Our analysis highlights the substantial ongoing burden of HIV-associated cryptococcal disease, primarily in sub-Saharan Africa. Cryptococcal meningitis is a metric of HIV treatment programme failure; timely HIV testing and rapid linkage to care remain an urgent priority.**

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Introduction

Cryptococcus is the most common cause of meningitis in adults living with HIV in sub-Saharan Africa.[1–3] Despite antiretroviral therapy (ART) expansion, prevalence of cryptococcal infection is largely unchanged in low-income and middle-income countries (LMICs), unlike in high-income countries (HICs).[4–7] Estimates of national, regional, and global burden of cryptococcal meningitis are crucial to guide prevention strategies and identify needs for diagnostic tests, antifungal medicines, and medical supplies, such as lumbar puncture needles and manometers.

In 2008, the global annual incidence of cryptococcosis was estimated as 957 900 cases per year (range 371 700–1 544 000 cases).[8] This estimate was based on published cohorts from the pre-ART era, and the wide range indicates the high level of uncertainty of these estimates. Since then, extensive ART expansion has occurred; AIDS-related deaths have reduced by 45% from 2·0 million to 1·1 million deaths.[9] The importance of asymptomatic cryptococcal antigenaemia as a precursor to symptomatic meningitis and death has been further defined,[10–13] and more cryptococcal antigenaemia prevalence data have been published.

WHO, US President's Emergency Plan for AIDS Relief, and US Department of Health and Human Services have recommended cryptococcal antigenaemia screening for people with a CD4-positive T-cell count of less than 100 cells per μL who are not receiving effective ART.[14–16] Cryptococcal antigenaemia screening coupled with pre-emptive antifungal therapy has a proven survival benefit,[10,12,17] and has been incorporated into HIV national guidelines in Botswana, Kenya, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, USA, and Zimbabwe with consideration elsewhere. Estimation of the cryptococcal disease burden helps stakeholders weigh the costs and resources required for hospital-based meningitis treatment versus investment of resources into a pre-emptive cryptococcal antigenaemia screen-and-treat strategy.[18] We aimed to provide an updated estimate of the global incidence of HIV-associated cryptococcal disease using published UNAIDS data for HIV incidence, ART access, retention in care, and published cryptococcal antigen prevalence data.

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Research in context

Evidence before this study

Cryptococcus is the most common cause of meningitis in adults in sub-Saharan Africa due to the burden of HIV infection. We searched PubMed with the terms "cryptococcal meningitis" and "burden" on Feb 8, 2017, with no restrictions on language or date. The only study to estimate the global burden of cryptococcal infection was published in 2008. The global annual incidence of cryptococcosis was estimated as 957 900 cases per year (range 371 700–1 544 000). This estimate was based on published cohorts primarily from the pre-antiretroviral therapy (ART) era, and the wide ranges indicate the high level of uncertainty of these estimates. This 2008 study used only three incidence publications to derive sub-Saharan African estimates.

Since then, extensive ART expansion has occurred; AIDS-related deaths have reduced by 39%. The importance of asymptomatic cryptococcal antigenaemia as a precursor to symptomatic meningitis and death has been further defined, and more cryptococcal antigenaemia prevalence data have been published.

Since the initial estimate of global burden of cryptococcal meningitis in 2008, small, retrospective studies describing the national burden of cryptococcal meningitis have been published in South Africa, Brazil, Ecuador, Nigeria, Tanzania, Kenya, Vietnam, Thailand, and USA. These studies used epidemiological, country-wide data from the local government, WHO, international and local reports, along with unreported data.

Added value of this study

This updated global estimate of cryptococcal infection is the first in 8 years. The landscape of HIV infection has changed greatly since the initial estimate of global burden. We provide an updated estimate of the global incidence of HIV-associated cryptococcal disease with published UNAIDS data for HIV incidence, ART access, retention in the care cascade and published cryptococcal antigenaemia prevalence data. Cryptococcal antigenaemia prevalence data have not been previously used to estimate incidence of cryptococcal meningitis.

Implications of all the available evidence

We estimated an average global cryptococcal antigen prevalence of 6% among HIV-infected people with a CD4 cell count of less than 100 cells per µL. Annually, 278 000 people have cryptococcal antigenaemia, with 73% of meningitis cases occurring in sub-Saharan Africa. Cryptococcal meningitis causes 15% of AIDS-related deaths globally, yet remains neglected by numerous stakeholders. This study summarises the global scale of disease and highlights the need to implement cryptococcal prevention efforts.

Methods

Global estimates of HIV infection

We used UNAIDS 2014 country-level estimates of global incidence and cases of HIV infection (table 1); specifically published estimates of adults (aged >15 years) living with HIV, adults receiving ART, percentage of adults receiving ART among those eligible per WHO 2010 guidelines (CD4 <350 cells per µL) via UNAIDS 2014 spectrum estimates,[24] UNAIDS GAP report,[9] and WHO Global Health Observatory database.[46] Each UNAIDS and WHO estimate was originally published with a low and high estimate range as a measure of uncertainty. Using the estimates of those with a CD4 cell count of less than 350 cells per µL on ART, and those eligible for ART, we calculated the ART gap (people who were not receiving ART but CD4 cell counts of <350 cells per µL). We used UNAIDS and WHO reports for estimates of the number of people with CD4 cell counts of less than 100 cells per µL,[19] CD4 cell counts of 100–200 cells per µL, virological failure,[26] and loss to follow-up (table 1, appendix pp 2–6).[26]

See Online for appendix

For each point estimate, a 95% CI was obtained. To further account for bias and limitations of the primary literature, the 95% CI was widened by adding or subtracting 1·5 times the difference between the right and left limits, respectively. Thus, the uncertainty ranges described in the Methods and in table 1 are conservatively wider than 95% CI from the published literature.

Estimate of people at risk for cryptococcal disease

We defined the total number of people at risk for cryptococcosis by country and region as: adults with a CD4 cell count of less than 100 cells per µL not on ART and adults with a CD4 cell count of less than 100 cells per µL on ART but either lost to follow-up or with virological failure. Those who start ART but do not have virological failure, and are negative for cryptococcal antigenaemia, have no risk of developing cryptococcal infection. The estimate of adults with a CD4 count of 100 cells per µL or less was 22·5% (range 19–26) among those with a CD4 cell count of less than 350 cells per µL in LMICs.[19,20] In HICs, 18·5% (range 16–21) of those with a CD4 cell count of less than 350 cells per µL were estimated to have a CD4 cell count of less than 100 cells per µL.[19,20] Thus, we estimated the number of patients with a CD4 count of less than 100 cells per µL on ART from the ART percentage coverage (ART percentage coverage×ART eligible [CD4 <350 cells per µL]×proportion with CD4 <100 cells per µL, accounting for uncertainty around those estimates; appendix pp 2, 3).

Based on a UNAIDS systematic review,[26] we assumed 16% (range 12–20) of people initiating ART retained in care had virological failure at 12 months. After completion of 1 year on ART, we assumed the virological failure incidence to be a third of that in the first year at 5·3% (95% CI 4·0–6·6).[26–29] This Article cites observational data from Canada, the USA, and the UK with similar frequencies of viral suppression at 12 months.[47–49]

Retention in care is based on country level estimates from UNAIDS,[24] and where data were missing, we used continental mean estimates.

Cryptococcal antigenaemia prevalence

We estimated the total number of people with cryptococcal antigenaemia using blood cryptococcal antigenaemia prevalence studies from 1989 to 2016, either in the published literature, or abstracts presented at conferences, among outpatient populations for 17 African countries, five Asian countries, five Latin American countries, the USA, and the UK (figure 1). Cryptococcal antigenaemia prevalence studies of solely inpatient populations were excluded because prevalence is higher in those presenting to the hospital and not representative of the asymptomatic outpatient population that is ideal for cryptococcal antigenaemia screening. For countries with available data, cryptococcal antigenaemia prevalence among people with a CD4 cell count of less than 100 cells per µL was used for that specific country along with the associated 95% CI by Fisher's exact test (appendix pp 4, 10). For countries without cryptococcal antigenaemia prevalence data, we used the pooled, weighted continental mean estimate. Thereafter, we estimated the number of people with prevalent cryptococcal antigenaemia by country and region by multiplying people at risk for cryptococcal disease by the cryptococcal antigenaemia prevalence of the country and region (described earlier and in table 1).

People positive for cryptococcal antigenaemia who develop cryptococcal meningitis

Not all patients positive for cryptococcal antigenaemia develop cryptococcal meningitis. Estimates of adults who are positive for cryptococcal antigenaemia who go on to develop symptomatic cryptococcal meningitis were from published cohort studies.[10–12,30–32] We estimated that 70% (range 56–84%) of people positive for cryptococcal antigenaemia would progress to develop cryptococcal disease or died without diagnosis, unless treated with ART or pre-emptive fluconazole (appendix p 6). Without ART or pre-emptive fluconazole therapy, we assumed 95% (uncertainty interval 90–100) progression in all regions (opinion of authors) with a 5% competing risk of death from other causes or comorbid conditions.[10,11,45,50,51]

People negative for cryptococcal antigenaemia who are at risk for cryptococcal infection

The cryptococcal meningitis incidence in people with a CD4 cell count of less than 200 cells per µL who were initially negative for cryptococcal antigenaemia in blood before initiating ART is 5·14 per 100 person-years.[30] This value is estimated from the only publication available for estimating incidence of cryptococcal meningitis before initiation of ART in Uganda, and for this estimation, we assumed an incidence range of 2·6–9·0 cryptococcal events per 100 person-years. In high-income countries, we assumed the risk of development of cryptococcal meningitis was 50% lower due to more intensive virological monitoring and additional second-line ART

	Estimate (uncertainty interval)
Adults living with HIV[19]	31·8 million (30·1–33·7)
Adults with CD4 <350 cells per µL[19]	19·5 million (18·5–20·7)
CD4 <100 cells per µL of those CD4 <350 cells per µL	
Low-income and middle-income countries[19–23]	22·5% (19–26)
High-income countries[19–23]	18·5% (16–21)
CD4 100–200 cells per µL of those CD4 <350 cells per µL	
Low-income and middle-income countries[19–23]	27·5% (24–31)
High-income countries	31·5% (29–34)
Adults receiving ART[19]	11·3 million (10·4–12·7)
New initiation of ART[19,24]	2·3 million (1·8–2·8)
Retention in care (year 1)*[25]	Country-specific, regional estimate, weighted pooled average; total LTFU estimated at 1·1 million in 2014
Virological failure	
Virological failure (year 1)[25,26]	16% (12–20)
Virological failure (year >2)*[27–29]	5·33% (4·0–6·6)
At risk for cryptococcal infection	CD4 <100 cells per µL not on ART CD4 <100 cells per µL on ART but LTFU or virological failure CD4 100–200 cells per µL not on ART, LTFU, or virological failure
CD4 100–200 cells per µL no ART, LTFU, or virological failure[10,30]	25% of those with CD4 <100 cells per µL not on ART, or LTFU, or virological failure
CRAG prevalence	
For countries with multiple sources	Weighted average of all sources and computed 95% CIs (figure 1)
For countries without sources	Regional weighted average (computed 95% CI)
CRAG-negative progression to CRAG-positive (without effective ART) CD4 <200 cells per µL	
Low-income and middle-income countries[30]	5·14 events per 100 person-years (2·6–9·0)
High-income country[30]	2·57 events per 100 person-years (1·3–4·5)
CRAG positive who develop cryptococcal meningitis	
In care without pre-emptive treatment[10–12,31,32]	70% (56–84)
Not in care[10–12,31,32]	95% (90–100)
Deaths from cryptococcal meningitis (1 year mortality)	
Low-income country[33–39]	70% (59–81)
Middle-income country[34,40–42]	40% (34–46)
North America[43,44]	20% (12·5–27·5)
Europe	30% (25–35)
Death not in care (all regions)[45]	1·5 times higher

For more information see appendix. ART=antiretroviral therapy. LTFU=lost to follow-up. CRAG=cryptococcal antigenaemia. *Retention-in-care and virological failure in more than 2 years were assumed to be 33% of their year 1 value.

Table 1: **Model inputs and assumptions**

Figure 1: **Cryptococcal antigenaemia prevalence studies of HIV-infected outpatient populations from 1989 to 2016**
Error bars are 95% CI, the vertical dotted line represents the mean cryptococcal antigenaemia prevalence for all studies combined. Estimates of USA and UK were not included in final summary estimate of low-income and middle-income countries. Studies of populations in hospital were not included (appendix p 11). All references for the studies in this figure are in the appendix. MSF=Médecins Sans Frontieres. N=north. SE=southeast. SW=southwest.

options. For people with CD4 less than 200 cells per µL, initially prevalent cryptococcal antigenaemia-negative status and not receiving ART, we assumed a competing risk of starting ART or death of 50% (ie, 500 of 1000 person-years).

Annual incidence of cryptococcal meningitis

Annual incidence of cryptococcal meningitis includes the estimation of those people positive for cryptococcal antigenaemia who developed symptomatic meningitis, both in care and newly initiating ART with unmasking

disease and those not in care or not on ART with AIDS progression.

Cryptococcal meningitis deaths

We estimated 1 year mortality in low-income countries (LICs) as 70% (uncertainty interval 59–81) after cryptococcal meningitis for those in care and 100% for those not in care (appendix p 5).[31,49,52–56] For middle-income countries, we presumed 1 year mortality of 40% (uncertainty interval 34–46), based on summary statistics of outcomes of those receiving amphotericin B and fluconazole, and 60% for those not originally in care (ie, not receiving ART).[40,41] In Europe (including eastern Europe and Russia), we estimated 1 year mortality to be 30% for those in care and 45% for those not in care (opinion of authors). In North America, we estimated 1 year mortality to be 20% for those in care and 30% for those not in care.[43]

Uncertainty analysis

To account for parameter uncertainty in the primary data, we used probability distributions to describe a range for each point estimate of interest. We varied each value in our model simultaneously, sampled from a priori defined probability distributions. The outputs from this uncertainty analysis generated CIs for each parameter. Full details of each parameter and distribution are available in the appendix (p 6).

We used empirical data, when available, to define distributions (appendix p 6). We used standard β distributions for binomial data, and normal distribution for continuous estimates. Using Microsoft Excel 2013, we randomly selected a value for each parameter within the appropriate distribution, and used the combination of these values to estimate the number of people positive for cryptococcal antigenaemia, annual incidence of cryptococcal meningitis, and number of deaths from cryptococcal meningitis for each region. Using 50 000 iterations, we obtained empirical distributions corresponding to posterior distributions calculated by Monte Carlo simulations. These distributions were used to generate a point estimate (posterior mean) and Monte Carlo CIs from the lower 2·5% and higher 97·5% for the estimates of cryptococcal antigenaemia, meningitis, and fatality from cryptococcal disease. Given the limited high-quality source data, we broadened our estimates of uncertainty of the primary data by widening our CIs to use 99·7% CI with three standard deviations above and below the weighted averages of included studies.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In December, 2013, 31·8 million (range 30·1–33·7) adults were living with HIV globally, with 21·7 million (20·7–23·0) living in sub-Saharan Africa. Globally, 19·5 million adults were eligible for ART (CD4 <350 cells per μL) according to

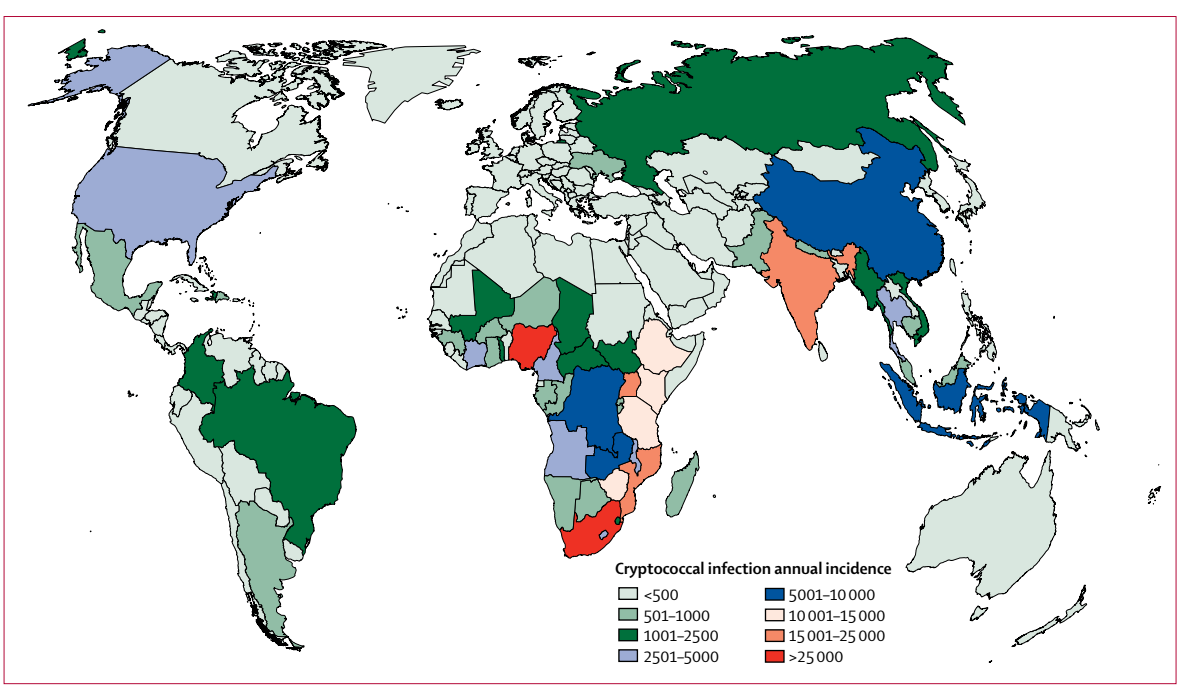

Figure 2: **Annual incidence of cryptococcal infection by country**
The annual number of people positive with cryptococcal antigenaemia estimated at 278 000 (95% CI 195 500–340 600) globally in 2014. We estimated 223 100 annual incident cases of cryptococcal meningitis in 2014..

WHO 2010 guidelines, with 11·3 million actually receiving ART. Globally, 8·2 million people had a CD4 count of less than 350 cells per μL but not receiving ART, with 5·2 million of these individuals in sub-Saharan Africa. We estimated 4·3 million adults have a CD4 count of less than 100 cells per μL globally, and of these, 1·8 million (42%) were not on ART. This group is at particularly high risk for opportunistic infections, including cryptococcosis. In 2013, there were an estimated 1·4 million (range 1·1–1·6) AIDS-related deaths globally, per UNAIDS estimates.

We estimated an average global cryptococcal antigenaemia prevalence of 6·0% (95% CI 5·8–6·2) in people with a CD4 count of less than 100 cells per μL, corresponding to 278 000 (95% CI 195 500–340 600) people globally in 2014 (figure 2). Annually, we estimated that there are 223 100 (95% CI 150 600–282 400) cases of cryptococcal meningitis globally, with 73% of cases (162 500 [95% CI 113 600–193 900]) occurring in sub-Saharan Africa (table 2; appendix p 9). The region with the second highest incidence was Asia and Pacific (19% of total), with an annual incidence of 43 200 (95% CI 25 300–64 700) cases of cryptococcal meningitis (table 2). Annual fatalities from cryptococcal meningitis are estimated at 181 100 (95% CI 119 400–234 300) deaths globally, with 135 900 (75%; 95% CI 93 900–163 900) deaths occurring in sub-Saharan Africa (table 2). Table 3 highlights countries with the highest annual incidence of cryptococcal meningitis. Globally, cryptococcal meningitis results in 15% of AIDS-related mortality (95% CI 10–19). The appendix provides country-level listing of data for all parameters considered in the model.

	Total cryptococcal antigenaemia positive (uncertainty interval)	Annual burden of cryptococcal meningitis (uncertainty interval)	Deaths from cryptococcal meningitis (uncertainty interval)
Sub-Saharan Africa	204 300 (148 400–237 800)	162 500 (113 600–193 900)	135 900 (93 900–163 900)
Asia and Pacific	52 300 (32 900–74 100)	43 200 (25 300–64 700)	39 700 (20 600–59 700)
Caribbean	1800 (1300–2200)	1400 (1000–1800)	700 (500–900)
Latin America	7000 (3600–11 100)	5300 (2600–8900)	2400 (1100–4400)
North America	3700 (3000–4600)	3000 (2300–3700)	700 (500–1000)
North Africa and Middle East	3600 (2600–5000)	3300 (2400–4500)	1900 (1300–2700)
Europe	5200 (4000–6500)	4400 (3400–5600)	1800 (1300–2400)
Global	278 000 (195 500–341 000)	223 100 (150 600–282 400)	181 100 (119 400–234 300)

Table 2: **Burden of cryptococcal infection by region**

	Annual incidence of cryptococcal meningitis	Number at risk (CD4 <100 cells per μL)	Cost of screening all at risk (US$)*	HIV budget to screen all at risk (%)[57]
Nigeria	27 100	325 900	$1 303 437	0·23%
South Africa	21 400	382 400	$1 529 685	0·09%
Mozambique	18 600	184 300	$737 228	0·28%
India	18 300	209 900	$839 502	0·06%
Uganda	12 200	110 500	$441 933	0·08%
Ethiopia	9600	60 600	$242 561	0·06%
Kenya	9000	84 700	$329 138	0·08%
Tanzania	8400	117 200	$468 959	0·15%
DR Congo	8400	51 200	$204 889	0·24%
Zimbabwe	8100	92 400	$369 621	..
Indonesia	6600	58 900	$235 564	0·27%
Zambia	5000	66 200	$264 611	0·10%

*Based on presumed cost of cryptococcal antigenaemia lateral flow assay test of US$3 per test delivered price for resource-limited areas, with an additional $0·50 added for laboratory labour, and $0·50 for profit and overhead costs. Although not every person at risk will present to care, this gives an estimate of the magnitude of budgetary resources necessary to start screening. Further information about each estimate is available in the appendix.

Table 3: **Countries with the highest incidence of cryptococcal meningitis**

Discussion

We estimated the global incidence of cryptococcal meningitis to be substantial at 223 100 cases annually (95% CI 150 600–282 400), resulting in 181 100 (95% CI 119 400–234 300) annual deaths in 2014. Sub-Saharan Africa continues to have the greatest burden of this disease. We estimated cryptococcal meningitis causes 15% (95% CI 10–19) of AIDS-related deaths globally. Although the absolute number of cryptococcal deaths has decreased since the previous 2008 estimate,[8] the proportion of AIDS-related mortality remains similar. Our estimates, and others, imply that cryptococcosis remains the second most common cause of AIDS-related mortality, only narrowly behind tuberculosis.[58–63] These updated accurate disease estimates enable appropriate ordering of essential antifungals, diagnostics, and medical supplies.

Importantly, prevention of cryptococcal disease has shown survival benefit and is cost-saving to health-care systems when coupled with enhanced ART adherence.[18,41,52,64] The cost of cryptococcal antigenaemia screening programmes needs to be appreciated in the context of the treatment costs for patients with cryptococcal meningitis in LMICs. For example, the per patient cost of cryptococcal meningitis treatment in Uganda with amphotericin B and fluconazole is US$400 for 2 weeks.[41] Consolidation and maintenance therapy with fluconazole for 1 year costs $60 per meningitis survivor ($0·15 per 200 mg fluconazole) in LMICs.[53] Thus, with an annual estimated incidence of 12 200 meningitis cases in Uganda, $5·6 million would be required for initial meningitis diagnosis and treatment. Conversely, if cryptococcal antigenaemia screening costs $4·00[54] plus $24·60 for the WHO-recommended pre-emptive treatment regimen,[9] screening the 110 500 people at risk for cryptococcal disease in Uganda with a CD4 count of less than 100 cells per μL and pre-emptively treating the 15 500 people positive for cryptococcal antigenaemia would cost $822 600, which is 15% of the cost of meningitis treatment with more than 40% better long-term survival.[33]

Compared with previous 2008 estimates,[8] our 2014 estimates are lower, because the HIV and AIDS

landscape has changed with rapid ART expansion and a 45% decrease in AIDS-related mortality from 2005 to 2013 in sub-Saharan Africa.[9] We also used a different method of cryptococcal antigenaemia prevalence, as cryptococcal antigenaemia positive status is a known predictor of progression to cryptococcal meningitis. Country-specific cryptococcal antigenaemia prevalence data were less available previously.

Additionally, we compared our estimates with the few published estimates of the national incidence of HIV-associated cryptococcal meningitis. Our model estimated that there are 2945 US cases of cryptococcal meningitis annually. In the USA, an estimated 3400 recognised cryptococcal meningitis admissions to hospital were identified by the International Classification of Diseases (9th edition) hospital billing codes, of which two-thirds were HIV-related.[43] In South Africa during 2015, the national reporting laboratory-confirmed 6174 cryptococcal meningitis cases and an additional 4295 people were positive for cryptococcal antigenaemia without documented meningitis.[5] W e estimated that there were 21 400 cryptococcal cases in South Africa for 2014. This discrepancy probably reflects a proportion of people living with AIDS not in care, undiagnosed, and lost to follow-up who do not receive a reported laboratory-confirmed diagnosis. An estimated 554 990 South Africans are living with AIDS,[5] and the median CD4 count in ART-naive people entering care was 150 cells per µL in 2015.[55] We estimated 382 400 South Africans with a CD4 count of less than 100 cells per µL would be at risk for cryptococcal disease. In 2015, the South African National Health Laboratory Service processed 360 000 specimens with CD4 counts of less than 100 cells per µL (about 10% of nationwide total) of which around 80% are estimated to be from unique individuals.[55]

One limitation of this estimate is our use of UNAIDS 2014 data,[24] when 2016 data are available.[65] The most recent figures were not used because the 2014 UNAIDS estimates have published numbers of people with a CD4 count of less than 350 cells per µL by country. We used these numbers to estimate a CD4 count of less than 100 cells per µL and thereby estimated the population at risk for cryptococcal infection. UNAIDS no longer publishes the number of people with CD4 counts of less than 350 cells per µL by country; thus, a 2016 estimate would require us to project this number with a CD4 count of less than 100 cells per µL based on the proportion of people who are HIV infected, thereby adding more uncertainty to our estimates. At the time of this publication, 2016 data were also missing in several important country estimates such as Nigeria and Ethiopia.

Further limitations of our analysis are related to the absence of UNAIDS country data for HICs. A second limitation is that many countries do not have any cryptococcal antigenaemia prevalence data available so estimates were extrapolated from countries in the region with cryptococcal antigenaemia data available. There is also substantial heterogeneity in studies reporting cryptococcal antigenaemia prevalence. Solely inpatient cryptococcal antigenaemia prevalence studies were excluded; however, some studies included symptomatic and asymptomatic people, which might overestimate point estimates for cryptococcal antigenaemia prevalence and yet underestimate the progression to symptomatic meningitis, if already symptomatic. Cryptococcal antigenaemia prevalence studies used different testing methods (latex agglutination *vs* lateral flow assay) with lower sensitivities for detection with latex agglutination. There are relatively few studies that have assessed progression of asymptomatic cryptococcal antigenaemia to symptomatic meningitis or death.[10–12,31,32] Our estimate of asymptomatic cryptococcal antigenaemia progression to symptomatic meningitis was based on a weighted average of mixed studies in which most people were not treated with antifungals at all.[11] Thus, progression to meningitis or death might be an underestimate and will vary with access to timely ART. To account for bias and limitations of the primary data, we did a probabilistic sensitivity analysis that generated Monte Carlo CIs according to the probability distribution of possible outcomes. Furthermore, our estimates of meningitis incidence and death are based on point-prevalence data over the past 10 years. These estimates do not reflect averages of historical trends nor are they based on dynamic disease models to predict future disease incidence. However, cryptococcal antigenaemia prevalence data have been relatively constant by country over time.[10,13,56] Notably, AIDS-related mortality due to cryptococcosis has remained stable from previous estimates.[8] However, with improvements in ART access and retention in care, estimates of incidence of cryptococcal meningitis should correspondingly decrease over time.

Despite global improvement in access to ART, the number of HIV-infected people with a CD4 count of less than 100 cells per µL is still substantial at about 20–25% of those presenting to care.[66] Thus, the annual number with cryptococcal infection is high at 278 000 globally. Cryptococcal meningitis is an excellent metric of HIV treatment programme failure. In 2016, no person with HIV should develop cryptococcal disease, yet due to challenges with late diagnosis, linkage to care, ART access, retention in care, and virological failure on ART,[20,66,67] the often final event in a failed cascade of HIV care is the development of cryptococcal meningitis. Until linkage to comprehensive HIV care can be improved, cryptococcal screening programmes are a worthy investment that identify populations at high risk for death. To reduce AIDS-related deaths, it is crucial to ensure that people with CD4 counts of less than 100 cells per µL are screened for cryptococcal antigenaemia, pre-emptively treated (if cryptococcal antigenaemia positive), and initiated on ART. In the

absence of initial CD4 testing, all people should be cryptococcal antigen screened.

Our analysis highlights the ongoing substantial burden of HIV-associated cryptococcal disease, primarily in sub-Saharan Africa but also in Asia and the Pacific. Timely HIV testing and rapid linkage to care is an urgent priority. Cryptococcal antigenaemia screening and pre-emptive fluconazole treatment should be part of a routine package of enhanced care for people presenting late with AIDS at time of entering into HIV care.

Contributors

RR searched the literature. RR, DRB, BJP, and RMS designed the study. RR and DRB collected data. RR, DRB, RMS, BJP, JNJ, NPG, TMC, DWD, and AL analysed data. RR, DRB, RMS, BJP, JNJ, NPG, TMC, DWD, and AL interpreted data. RR and DRB wrote the Article.

Declaration of interests

DWD and family hold founder shares in F2G Ltd, in Novocyt. DWD acts or has recently acted as a consultant to Astellas, Sigma Tau, Basilea, Scynexis, Cidara, Biosergen, Quintilles, Pulmatrix, and Pulmocide. DWD has been paid for talks on behalf of Astellas, Dynamiker, Gilead, Merck, and Pfizer. DWD is a long-standing member of the Infectious Disease Society of America Aspergillosis Guidelines group, the European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines group, and the British Society for Medical Mycology Standards of Care committee. DWD has a patent in assays for fungal infection licensed. NPG received grants from National Institutes of Health (NIH), another from MSD, personal fees from Fujifilm Pharma and Astellas, grants from Centers for Disease Control and the National Health Laboratory Service Research Trust, outside of this Article. DRB received grants from NIH and UK Medial Research Council, during the conduct of the study. JNJ received grants from Gilead Sciences Europe, outside of the Article. All other authors declare no competing interests.

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