**Cryptococcal Meningoencephalitis: Time For Action**

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**Word Count: 4339**

**Key Words**

Cryptococcus

Cryptococcal meningitis

Neglected diseases

Low- and middle-income countries

People living with HIV

Antifungal therapeutics

Advanced HIV disease

**Summary**

Cryptococcal meningoencephalitis was first described over a century ago. It is preventable and treatable yet continues to be associated with excessive morbidity and mortality. The largest burden of disease resides with people living with HIV (PLHIV) in low- and middle-income countries (LMICs). In this group, mortality with the best antifungal induction regimen (seven days of amphotericin B deoxycholate (1.0 mg/kg/day) and flucytosine (100 mg/kg/day)) in a clinical trial setting is 24% at 10 weeks. The world is now at an inflection point in terms of recognition, research and action to address the burden of morbidity and mortality from cryptococcal meningoencephalitis. However, the scope of programs needs to increase, with particular attention to implementation science that is specific to individual countries. This review summarises causes of excessive mortality, interventions with demonstrated survival benefit, and gaps in knowledge and practice that contribute to the ongoing high death toll from cryptococcal meningoencephalitis.

**Cryptococcal Meningoencephalitis**

Cryptococcosis is an invasive fungal disease caused by the ubiquitous basidiomycete yeasts *Cryptococcus neoformans* and *Cryptococcus gattii*.1 *C. neoformans* is responsible for 95% of human cryptococcal disease,2 although *C. gattii* is increasingly recognised as a pathogen of global relevance.3,4 Cryptococcosis encompasses a spectrum that ranges from latent infection, through subclinical disseminated disease, to fulminant meningoencephalitis. The latter occurs commonly in the setting of advanced immunosuppression and is uniformly fatal without antifungal therapy.5

Cryptococcal meningoencephalitis is frequently associated with advanced HIV disease (AHD),6 in which context it causes an estimated 223,000 incident cases per year and 180,000 deaths. Cryptococcal meningoencephalitis also occurs in solid-organ transplant recipients, patients with malignancy and other immunosuppressive conditions, as well as in apparently immunocompetent hosts.7 Clinical manifestations include headache, seizures, cranial nerve abnormalities and altered mentation, which often progresses to coma and death. In survivors, 69% of PLHIV and 73% of non-HIV patients suffer cognitive and/or physical impairment 12 months after diagnosis.8,9 More than a third of patients report difficulty or inability to work 6 months after diagnosis.8 A number of recent scientific and policy advances have contributed to improved identification and management of patients with cryptococcal meningoencephalitis worldwide. However, much remains to be done.

**Efforts to control the HIV/AIDS epidemic have not reduced the global burden of cryptococcal meningoencephalitis**

Surveillance data from Botswana10 and South Africa11,12 suggest that despite excellent population antiretroviral therapy (ART) coverage, the incidence of cryptococcal meningoencephalitis remains high. A reduction in the number of patients presenting to HIV services *de novo* with low CD4+ cell count has been offset by an increase in individuals presenting with advanced immunosuppression having defaulted or failed ART. The characteristics of patients presenting with cryptococcal meningoencephalitis has shifted from primarily ART-naïve, to > 50% being ART-experienced12-14. Therefore, while regions of high HIV prevalence bear a high burden of mortality from cryptococcal meningoencephalitis, expanded access to widespread HIV treatment appears insufficient to substantially reduce cryptococcal deaths (Figure 1).

To markedly reduce mortality from cryptococcal meningoencephalitis, HIV care cascades must be strengthened to sustain virological suppression at population level. In parallel, there must be focus on early diagnosis of cryptococcal meningoencephalitis. Development of novel therapeutic strategies is urgently required. Interventions with proven survival benefit must be implemented within routine clinical care, which in many settings requires better funding, staffing, training and access to commodities. More broadly, the social and health system challenges that contribute to mortality must be addressed.

**Clinicopathological Correlates of Death**

*Early Detection and Management of Cryptococcal Infection Reduces Mortality*

The development of a simple, cheap and accurate point-of-care lateral flow assay (LFA) for CrAg has been a significant advance for detection of pre-symptomatic cryptococcal infection. CrAg is detectable in blood 6 to 7 months before the onset of symptoms and independently predicts meningitis and death.29,30 The REMSTART trial showed that in conjunction with adherence support, CrAg-based screening and antifungal treatment can reduce mortality in people with AHD initiating ART by 28% compared to standard clinic-based care alone (p=0.004).31 Decision-tree modelling has predicted that universal CrAg screening and pre-emptive fluconazole therapy for PLHIV with CD4 <100 cells/μl would avert 25 disability-adjusted life years (DALYs) per 100 participants, at a cost of US$6.14 per DALY.32 The comparable figure for cost per DALY averted for PLHIV on ART prescribed 9 months of isoniazid tuberculosis preventive therapy (IPT) is US$266.33 Both calculations are based on PLHIV in Ugandan HIV clinics and on 2016/ 2017 US$.32,33 A CrAg-based ‘screen-and-treat’ strategy is recommended by the World Health Organisation (WHO) for PLHIV with CD4+ counts <100 cells/mm3 (and should be considered for CD4+ <200 cells/mm3).34 Although implementation and scale up of screen-and-treat programs has been slow, they are now operational in more than 25 countries worldwide. Nevertheless, the lack of universal coverage remains a significant obstacle to reducing the incidence of cryptococcal meningoencephalitis.35

To capitalise on the potential survival benefit presented by screen-and-treat programs, there are three key areas in need of further research. First, innovative therapeutic strategies are urgently required for CrAg-positive individuals identified through screening. Between 13 and 25% of asymptomatic CrAg-positive patients fail pre-emptive fluconazole therapy, proceeding to clinical cryptococcal meningoencephalitis or death by 6 months.31,36,37 The ongoing ACACIA trial (NCT03945448) compares a single dose of liposomal amphotericin B (LAmB; 10 mg/kg) plus fluconazole, to fluconazole alone for asymptomatic cryptococcal antigenaemia. An oral combination of flucytosine and fluconazole may be an alternative and this will be investigated in the EFFECT trial (personal communication, JNJ and TSH). Second, implementation research is needed to identify local barriers to implementation of CrAg screening, obstacles to treatment adherence and strategies to improve loss to follow-up. Third, the role of semiquantitative CrAg assays in stratifying patients requiring urgent investigation for CNS disease or more intensive pre-emptive therapy requires further investigation.34,38

*Clinical Signs Provide Clues to Pathology*

Once CNS disease is established, a high fungal burden in cerebrospinal fluid (CSF) and baseline alterations in mental status are two independent predictors of mortality from cryptococcal meningoencephalitis.39 While data directly linking either seizures at baseline or increased intracranial pressure (ICP) at baseline with mortality are inconsistent, these clinical features are themselves associated with higher CSF fungal burden and altered mental status.39-41 A greater fungal burden in CSF is likely to reflect higher cryptococcal density in the brain parenchyma and central nervous system (CNS) as a whole. The term meningoencephalitis is more accurate than meningitis because it acknowledges the propensity for involvement of brain parenchyma and ventricles as well as the meninges.42,43 Large cryptococcomas are characteristic of cryptococcal meningoencephalitis in AHD42 and especially infection with *C. gattii*.44

*The Significance of Raised Intracranial Pressure*

The large burden of fungal cells in and around the brain increases CSF viscosity, obstructs CSF flow and impedes CSF reabsorption.45 Cerebral oedema results from dramatic increases in ICP, with pressures >250 mm CSF in 51 – 56% of cases.46 Clinical manifestations include headache, cranial nerve abnormalities and reduced level of consciousness.

Raised ICP must be managed aggressively with antifungal therapy and repeated CSF drainage. Serial lumbar punctures (LPs) performed during the first 14 days of therapy mitigate the association between raised baseline opening pressure and mortality.47,48 Importantly, accurate recording of raised ICP requires a manometer – a simple cylinder attached to a three-way tap that fits onto the end of an LP needle. This basic equipment is almost universally unavailable in LMICs and some groups have devised innovative alternative methods of ICP measurement, including using intravenous tubing sets49 and the less accurate but more available method of counting drops of CSF flowing from a spinal needle.50 In the absence of any means of measuring ICP, removal of a pre-defined volume of CSF is a contentious strategy since large falls in pressure can be difficult to predict.51

*Rapid Reduction in Fungal Load is Paramount*

The rate of decline of fungal burden with antifungal treatment is linked with the risk of death.39,48 Early fungicidal activity (EFA) (i.e. a linear regression of log10 colony forming units (CFU)/mL vs. time) is routinely used as a primary endpoint for Phase II clinical studies and a secondary endpoint in Phase III trials.14,52,53 A pooled analysis of individual-level CSF data from 738 subjects suggests that an EFA <0.20 Log10CFU/mL/day versus >= 0.20 Log10CFU/mL/day is associated with a hazard ratio for 18-week mortality of 1.60 (95% CI, 1.25 – 2.04, p=0.002).54 Similarly, in a combined analysis of 501 ART-naïve patients, EFA values > 0.2 Log10CFU/mL/day were associated with the greatest probability of survival.55

**People die of cryptococcal meningoencephalitis due to suboptimal antifungal therapy**

Just three antifungal agents (amphotericin B deoxycholate (DAmB), flucytosine and fluconazole) are widely available for the treatment of HIV-associated cryptococcal meningoencephalitis in LMICs. The most effective regimen in terms of fungicidal activity and mortality is a combination of DAmB and flucytosine, with the combination of fluconazole and flucytosine an alternative.14,53,56 The combination of DAmB and fluconazole is less efficacious.14

At present, most healthcare systems worldwide that manage patients with cryptococcal meningoencephalitis do not have the resources to deliver effective antifungal therapy, which is predicated on a rapid and sustained reduction in fungal load within the CNS. An improved understanding of the pharmacokinetics and pharmacodynamics of polyenes has enabled a number of innovative induction regimens. The ACTA trial demonstrated the non-inferiority of one week of DAmB (1 mg/kg/day) plus flucytosine (100 mg/kg/day) followed by 7 days of fluconazole (1200 mg/day) versus regimens based on two weeks of DAmB, in terms of mortality at ten weeks14 and one year.57 The ongoing AMBITION trial tests this approach further by exploiting the relative safety of LAmB, testing induction therapy with a single high dose of LAmB (10 mg/kg) plus 14 days of fluconazole (1200 mg/day) and flucytosine (100 mg/kg/day).58

Flucytosine is an essential component of effective induction regimens for cryptococcal meningoencephalitis. Combined with DAmB, flucytosine produces more rapid fungicidal activity than fluconazole and enables abbreviation of the course of amphotericin B, thereby minimising toxicity.14,53 The intrinsic superiority of flucytosine over fluconazole in DAmB-based regimens is probably multifactorial and related to drug penetration into the CNS,59 a long post antifungal effect60 and pharmacodynamic synergism between polyenes and flucytosine.61

Despite clear evidence of the superiority of regimens containing flucytosine and/or DAmB, many patients with cryptococcal meningoencephalitis are treated with fluconazole monotherapy. Mortality rates are 40-70% with this approach.62-65 Recent clinical data provide evidence of the acquisition of fluconazole-resistant cryptococcal subpopulations from the environment, and their expansion on fluconazole monotherapy (800-1200 mg/kg/day).66 Combination therapy with fluconazole (1200 mg/kg/day) and flucytosine (100 mg/kg/day) kills these resistant subpopulations within 14 days.66 Even among patients infected with wild type strains of *Cryptococcus* spp., approximately half are predicted to fail monotherapy with fluconazole (1200 mg/day) because they will not generate sufficient drug exposure to prevent the emergence of resistant clones.67

There are multiple reasons neither flucytosine nor DAmB are routinely administered in LMICs. First, there is lack of access to both drugs.68 Flucytosine is unregistered in the vast majority of LMICs and throughout Africa.69,70 The price of flucytosine has historically been prohibitive due to manufacturer pricing monopoly71 and a perception that profit margins from LMICs do not justify the resources required to scale up manufacturing.69 In turn, this has contributed to a lack of demand for flucytosine from practitioners who are unfamiliar with the drug.69,70 However, there is recent cause for optimism. In the AMBITION trial, flucytosine is being procured for approximately US$ 180 for a 2-week course.72 At this price, the combination of flucytosine and fluconazole is cost-effective in sub-Saharan Africa compared with fluconazole monotherapy when hospital care costs and mortality are also considered (incremental cost-effectiveness ratio (ICER) US$65 per life-year saved).73 Furthermore, the global pharmaceutical company Mylan has received WHO prequalification for flucytosine, which will facilitate accelerated registration in LMICs74 and Strides, a generic manufacturer, has received US Food and Drug Administration (FDA) approval for the drug.75 UNITAID have announced a programme to support use of flucytosine and LAmB in 7 African countries.76 In South Africa, flucytosine is available for routine use in the Western Cape and at a number of tertiary centres, with early indications of a subsequent fall in in-hospital mortality.69

For the most effective regimen of 1 week of DAmB plus flucytosine for induction therapy,14 the ICER per life-year saved in sub-Saharan Africa is US$208.77 While DAmB is frequently licensed for use in LMICs,68 it remains unaffordable or unavailable in much of Africa. Training for safe DAmB administration is scarce and funding and procurement uncoordinated.70 Access is somewhat better in Asia, where regional generic manufacturers can produce DAmB.34 However, there are indications of progress. Amphotericin B formulations, flucytosine and fluconazole are now included in the WHO Model List of Essential Medicines.78 The availability of LAmB should increase in 116 LMICs in response to an access initiative from Gilead Sciences.79 The ARV Procurement Working Group (APWG), whose members include CHAI, PEPFAR, The Global Fund and 3 offices of the United Nations, recently expanded its scope to include LAmB, DAmB and flucytosine in its list of monitored products.80

The second barrier to effective antifungal therapy in LMICs is the inability to monitor and manage life-threatening adverse events. This is especially the case for DAmB, which can cause dose-related nephrotoxicity, electrolyte derangements leading to cardiotoxicity, and direct suppression of erythropoiesis resulting in severe anaemia.81,82 Pharmacokinetic data suggest that dosages of DAmB that approach 1 mg/kg/day cause enough toxicity to offset mortality gains made in terms of CSF sterilisation.83 While DAmB dosages approaching 1.0 mg/kg/day have not been directly compared in monotherapy in a clinical trial, 0.7 mg/kg/day and 1 mg/kg/day have been compared in combination with flucytosine (100 mg/kg/day).84 The 1 mg/kg/day dosage was associated with higher EFA but not with a reduction in mortality.84 Abbreviated amphotericin B-based regimens are hoped to improve the balance between fungicidal efficacy and tolerability.14,58

The option of an all-oral regimen of flucytosine and fluconazole mitigates some of the risks of parenteral drug administration. The safety profile of flucytosine compares favourably to DAmB, although it can cause dose-dependent bone marrow suppression and hepatotoxicity.85 Fluconazole undergoes extensive metabolism in the liver and can (rarely) cause reversible hepatocellular toxicity.

Thirdly, the prospect of effective antifungal therapy is limited by polypharmacy, most frequently with ART and anti-tuberculosis medications. Drug interactions are common. Rifampicin reduces the area under the concentration-time curve of fluconazole by 22%,86 limiting the likelihood of fluconazole pharmacokinetic target attainment. The potential for additive toxicity underscores the obligation to monitor renal and hepatic function, possibly for months - for example with IPT and long term fluconazole.87 The pill burden for patients taking prolonged therapy for polymicrobial infection is onerous and suboptimal adherence is common.31

**Patients Die Because of an Inability to Predict and Manage Immunological Dysregulation**

*The role of inflammation in pathogenesis is complex*

Survival from cryptococcal meningoencephalitis depends on a balanced inflammatory response - sufficient to clear the fungus, but not so much that it induces collateral damage to the host (see the damage-response framework of microbial pathogenesis).88,89 A parabolic relationship exists such that host damage is maximal in response to both the weakest and the strongest immune responses.89 The inability to predict where an individual is located along the damage-response framework parabola renders the design of interventions to control the host response fraught with uncertainty.88,89

*The potential of immunological adjuncts to standard antifungal therapy has not yet been realised*

In patients with a first episode of HIV-associated cryptococcal meningoencephalitis, low baseline levels of pro-inflammatory cytokines (i.e. interferon (IFN)-γ, tumour necrosis factor (TNF)-α and interleukins 2, 6, 8 and 17) are associated with increased mortality.39,90,91 Conversely, an early pro-inflammatory response and classical macrophage activation imparts an EFA and mortality benefit.90-93 In HIV-seronegative patients, there may be a relatively strong cellular immune response in the CNS with abundant pro-inflammatory cytokines, but dysfunctional phagocytosis.94

Interventions designed to augment the host response are not in routine use. Two clinical trials have demonstrated that administration of IFN-γ in combination with amphotericin B promotes inflammation, increases fungal clearance from CSF and produces a trend towards improved survival in HIV-associated cryptococcal meningoencephalitis.93,95 However, this has not been tested in Phase III clinical trials. Further work is needed to select those patients most likely to benefit - likely those with minimal endogenous IFN-γ responses.96 The use of monoclonal antibodies directed against cryptococcal capsular polysaccharide presents another promising approach. One such antibody, 18B7, was well tolerated up to doses of 1 mg/kg in a Phase I clinical trial97 although no efficacy data currently exist.

Concerns related to an overly exuberant immune response have prompted the use of anti-inflammatory agents. There are case reports of corticosteroids reducing raised ICP and/or improving neurological sequelae in non-HIV cryptococcal meningoencephalitis 98-100. In contrast, the use of dexamethasone is detrimental as an adjunct to antifungal therapy in PLHIV. While it does reduce ICP in this population, it is associated with rapid early declines in TNF-α in CSF,101 slower clearance of *Cryptococcus* spp. from CSF, increased morbidity and probably excess mortality.52

*IRIS is a persistent problem*

Cryptococcal IRIS is an important cause of death. IRIS occurs in 10-20% of cryptococcal meningoencephalitis patients during immunological restoration on ART102-104 and in 5-12% of solid-organ transplant recipients.105 Risk factors in the non-HIV population include rapid reduction in immunosuppressive therapy - in particular, discontinuation of calcineurin inhibitors – and resolution of immunosuppressive disorders.105-107 In apparently immunocompetent individuals, a post-infectious inflammatory response syndrome (PIIRS) has been described, characterised by non-recovery of mental status despite sterile CSF.108

Most of the description of cryptococcal IRIS derives from HIV-associated disease. Prior to ART initiation, in patients who go on to develop IRIS, there is a paucity of inflammatory cytokines in the CNS.109-111 During immunological reconstitution, there is CNS recruitment of monocytes and T cells.112,113 However, these immunological effectors fail to completely clear the inciting antigen,103,110 leading to persistently increased levels of proinflammatory biomarkers including C-reactive protein and D-dimer.103,114 The ensuing inflammation mimics uncontrolled fungal infection with neurological signs and symptoms and raised ICP. Early ART initiation is associated with CNS cellular infiltrate, macrophage/microglial activation and increased mortality, compared with late ART initiation (1-2 weeks versus 4-6 weeks after diagnosis of cryptococcal meningoencephalitis).115 ART initiation should be deferred in cryptococcal meningoencephalitis patients if there is any risk of rapid CNS immune reconstitution based on their ART history.116 In solid-organ transplant recipients, reduction of immunosuppression is thought to promote a switch from a medically-induced Th2 dominant immunophenotype to a Th1 proinflammatory response, triggering a clinical picture comparable to that seen in PLHIV.114 In apparently immunocompetent patients with PIIRS there is T-cell inflammation and axonal damage but an intact IFN-γ response.108

Treatment of IRIS remains unsatisfactory. Uncertainty about the possibility of an incompletely treated fungal infection (CrAg can remain positive for years after successful treatment, and cryptococcal culture can take 14 days) often promotes long courses of induction antifungal therapy. The only agents with which there is experience for treatment of IRIS are corticosteroids,106,117 which are at best imprecise agents for rebalancing immune function. Large prospective studies involving longitudinal clinical, microbiological and immunophenotypic characterisation of subjects are required to define immune pathways amenable to safe and predictable intervention.118

**A complex medical and social context**

*Cryptococcal meningoencephalitis is a manifestation of a severely impaired host*

Advanced stages of HIV are associated with a range of debilitating and interrelated conditions including chronic diarrhoea, oesophageal candidiasis, malnutrition, disseminated mycobacterial and viral infections, recurrent sepsis, pneumonias and non-cryptococcal mycoses.119,120 At autopsy, patients with confirmed cryptococcal infection display evidence of multiple concomitant life-threatening conditions, such that the immediate cause of death is difficult to distinguish.37,120 Of 514 patients with cryptococcal meningoencephalitis in Cape Town, 10 (1.9%) had microbiologically-confirmed dual CNS infection with tuberculosis, syphilis or bacterial meningitis.121

*Cryptococcal meningoencephalitis occurs where society is stretched*

Delays to diagnosis are common in settings where resources are limited. Caring and family responsibilities, logistical challenges related to travel and opportunity costs impede early presentation to health services. Psychosocial factors are often-overlooked but potentially important contributors to late presentation.122 For patients who are able to reach a healthcare facility, a CSF India Ink preparation is positive in 70-90% of cases,39 but this depends on diagnostic laboratory facilities and expertise. In contrast, the sensitivity and specificity of the CrAg LFA in serum are up to 100% and 99.5%, respectively, and in CSF 99.3% and 99.1%, respectively.123,124 Thus, for diagnosis as well as pre-emptive screening, the availability of this assay is essential to improve outcomes from cryptococcal meningoencephalitis.

*Mortality from cryptococcal meningoencephalitis is a symptom of under resourced healthcare systems*

High quality supportive care is difficult to provide in settings where nursing staff are scarce. For comparison, per 10,000 population, there are 81.72 and 28.12 nursing staff and doctors, respectively, in the UK, 13.08 and 9.05 in South Africa and 4.39 and 0.36 in Malawi.125 Patients with cryptococcal meningoencephalitis are medically complex and often have reduced conscious level. Optimal care requires administration of intravenous therapy, frequent neurological observations, serial LPs and prevention of clinical complications. Concomitant opportunistic infections must be screened for and managed.

In 2017, the WHO recommended a package of care for patients with AHD (CD4 cell count <200 cells/mm3 or WHO stage 3 or 4 event).126 The package includes CrAg screening, tuberculosis screening plus IPT, co-trimoxazole prophylaxis, guidelines on ART initiation and tailored adherence counselling. In 2019, UNITAID invested US$ 20 million in measures implemented by Clinton Health Access Initiative (CHAI) intended to widen access to these packages through partnership with civil society, academia, governments, non-governmental organisations and other global health partners.76 Médecins Sans Frontières (MSF) and the Elizabeth Glaser Paediatric AIDS Foundation are among those organisations with AHD care package programs.127 These initiatives are being rolled out in 7 LMICs this year. However, the task is not trivial. Implementation must be supported by clinical and laboratory facilities, training, supervision, clinical escalation protocols, mobile outreach and follow up capacity. Evaluation of implementation will be central to refining models that can be scaled up by national administrations and other funding bodies.76

**Thinking outside of the triangle; alternatives to amphotericin B deoxycholate, flucytosine and fluconazole**

The drug pipeline for cryptococcal meningoencephalitis has historically been slow to progress. Clinical trials of repurposed drugs such as sertraline128 and tamoxifen129 as adjuncts to polyene-based therapy have been disappointing. An ideal antifungal candidate for cryptococcal meningoencephalitis would exhibit at least equal potency to amphotericin B, with an improved safety profile and oral administration. Thankfully, a number of promising novel agents are in development (table 1). In addition, a project run by the Drugs for Neglected Diseases Initiative (DNDi) with European and African partners that aims to develop a modified-release formulation of flucytosine was initiated in July 2020.140 Neurapheresis is a novel technique under study designed to reduce CSF fungal burden and control ICP using extracorporeal filtration of CSF.141 This may prove to be a treatment option in well-resourced settings.

It is key that the effort committed to these novel developments is translated into tangible clinical benefits. In 2018, cryptococcal meningoencephalitis was added to the FDA list of tropical diseases that qualify for a priority review voucher.142 The WHO prequalification scheme aims to support national authorities through quality assurance. Crucially, existing and novel drugs for cryptococcal meningoencephalitis must be affordable to the countries that bear the burden of cryptococcal meningoencephalitis to be effective in a real-world sense.

**Challenges and Opportunities**

The burden of mortality from cryptococcal meningoencephalitis is huge. While at an individual patient level, the reasons for death are undeniably part of a larger picture of advanced immunosuppression, there are widespread systematic failings that contribute to excessive mortality. These include health system challenges, failures in the development and delivery of therapeutics and a lack of implementation capacity commensurate with the burden of suffering and mortality from this disease (Figure 2). Best treatment practices remain aspirational for many countries. Interventions with proven mortality benefit such as repeated therapeutic LPs and administration of amphotericin B and flucytosine are either unfeasible or unavailable in LMICs. Even in middle- and high-income countries, mortality rates of 20-40% persist.6 Contrary to widespread assumption, funding for cryptococcal meningoencephalitis does not fall within the remit of HIV funding, despite being the second most frequent cause of HIV-related deaths after tuberculosis.6 Since it does not meet WHO criteria for recognition as a neglected tropical disease, it does not receive funding from this route either.143 In 2018, cryptococcal meningoencephalitis received just 0.2% (7.7 million US$) of available relevant research and development funding, compared with 17% (684.6 million US$) of funding directed towards R&D for tuberculosis.144

Importantly, we are now at an inflection point in terms of recognition, funding, research and action to address the burden of morbidity and mortality from cryptococcal meningoencephalitis. Implementation of the LFA and trials of novel treatment regimens are essential developments that are specifically designed for implementation in the clinical settings of greatest need.14,58 The WHO has increased the strength of its recommendation for CrAg screening in at-risk populations.34 Examples of country-specific training in the prevention and management of cryptococcal meningoencephalitis now exist.145 The ACTA trial results were swiftly incorporated into WHO guidelines.34 Considerable advocacy efforts by the cryptoMAG consortium, MSF and others have played a large role in numerous significant policy advances.70,146 Cryptococcal meningoencephalitis has been declared a neglected disease in the G-finder report, highlighting the need for affordable, efficacious drugs suitable for resource-poor settings.147 The DREAMM trial (NCT03226379) is implementing packages of tests and treatment for HIV-related meningoencephalitis in Tanzania, Malawi and Cameroon. The APWG now lists flucytosine, LAmB and DAmB among its monitored products.80 The anti-cryptococcal drug development pipeline is more promising than it has been in a generation.

The cryptococcal research and advocacy community is small but active. The current era is characterised by innovation and momentum in terms of novel technologies and treatment strategies that are designed to be feasible in LMICs. It is imperative that this momentum is maintained and links with funders, large scale implementers and ministries of health strengthened. Specific priority targets for action are outlined in table 2. While there is room for cautious optimism in considering the future for patients with cryptococcal meningoencephalitis, this is no time for complacency. The advances that have been made must be viewed as the start of a new era – significant needs remain unmet and until they are addressed, people will continue to die in the hundreds of thousands from a preventable and treatable disease.

**Search strategy and selection criteria**

We searched PubMed and Google Scholar for articles published up to June 30, 2020, using the terms “cryptococcal meningitis”, “cryptococcal meningoencephalitis”, “HIV-associated meningitis” or “cryptococcosis”, in combination with “mortality”, “incidence”, “prevalence”, “screening”, “drug\*”, “therapy”, “treatment” or “IRIS”. We reviewed these articles, and relevant articles in the references of these articles. No language restrictions were applied. We consulted experts in the field to identify additional relevant studies, advocacy groups, and policy advances.

**Acknowledgments**

KES is a Wellcome Trust Clinical PhD Fellow (203919/Z/16/Z). JND has received grant funding from the Wellcome Trust, the UK Medical Research Council, the UK Department for International Development, The National Institutes for Health, The British Medical Association, the Li Ka Shing Foundation and the British Infection Society. WH holds awards from the Medical Research Council, National Institute of Health Research, FDA and the European Commission. JNJ holds grant funding from the Wellcome Trust, the UK Medical Research Council, the UK Department for International Development, the Swedish International Development Agency, the National Institutes for Health, and the U.K. National Institute for Health Research (NIHR) using Official Development Assistance (ODA) funding through a Global Health Professorship (grant RP-2017-08-ST2-012). The views expressed are those of the authors and not necessarily those of the NHS, NIHR, or the Department of Health and Social Care.

**Contributors**

KES and WH conceived this Review. KES performed the initial literature search, wrote the first draft of the manuscript and designed and drafted the tables and figures. All authors contributed to, reviewed and approved the final draft.

**Declaration of interests**

KES, AL, MA, TH, HCM, DGL – Nil

TB has received research funding from Gilead sciences and speaker fees from Gilead Sciences and Pfizer. JND has received fees for scientific consulting for Viamet Pharmaceuticals. JRP has research grants and performs consultation for Astellas, Pfizer, Merck, F2G, Amplyx, Matinas, Scynexis, Appili and Minnetronix. WH holds or has recently held research grants with F2G, Astellas Pharma, Spero Therapeutics, Antabio, Allecra, Bugworks, and NAEJA-RGM. WH has received personal fees in his capacity as a consultant for F2G, Amplyx, Ausperix, Spero Therapeutics, VenatoRx, Pfizer and BLC/TAZ.

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Key messages

* High population-level antiretroviral coverage is necessary but insufficient to significantly reduce the huge burden of mortality from cryptococcal meningoencephalitis.
* At present, most healthcare systems worldwide that manage patients with cryptococcal meningoencephalitis do not have the resources to deliver effective antifungal therapy.
* Interventions designed to manipulate the immune response to *Cryptococcus* spp. are not in routine use due limited understanding of which immune pathways to target, which patients will benefit and a lack of efficacy data.
* Implementation research is urgently needed to support the roll out of interventions with proven mortality benefit such as universal CrAg-screening programmes and serial lumbar punctures.
* International funders and policy makers are currently taking considerable positive steps to improve care for patients with cryptococcal meningoencephalitis worldwide.
* For the first time in decades, a number of promising novel therapeutic agents are in the development pipeline for cryptococcal meningoencephalitis.
* The current era of increased action is welcome and overdue but must be expanded in scope and magnitude to achieve significant reductions in mortality from cryptococcal meningoencephalitis.

**Table 1: Potential drugs in development for cryptococcal meningoencephalitis**

CME: Cryptococcal meningoencephalitis; PK: pharmacokinetic; PD: pharmacodynamic; AmB: amphotericin B; BID: *bis in die* (twice per day); IV: intravenous; FDA: Food and Drug Administration. QIDP: Qualified Infectious Disease Product.

**Table 2 Priority targets to reduce mortality from cryptococcal meningoencephalitis**

LMICs: Low- and middle-income countries; AHD: advanced HIV disease; CrAg: cryptococcal antigen; LAmB: liposomal amphotericin B.

**Figure 1: ART coverage is not sufficient to reduce mortality from cryptococcal meningoencephalitis in resource-limited settings**

Cryptococcal meningoencephalitis mortality reported from observational studies. GDP, ART coverage and HIV prevalence reported from time of data collection. Data from 15-28. ART: antiretroviral therapy. GDP: Gross domestic product. While there is no association between ART coverage and % mortality from cryptococcal meningoencephalitis, there is a trend towards higher mortality with increased HIV prevalence, and a significant negative association between GDP and mortality. Mortality from cryptococcal meningoencephalitis results from a complex interplay of factors related to poverty, and ART coverage alone is insufficient to reduce it.

**Figure 2: Contributors to mortality from cryptococcal meningoencephalitis**

CNS: Central nervous system; ICP: intracranial pressure; IRIS: immune reconstitution inflammatory syndrome