Trends in Cryptococcal Meningitis Mortality Using Routine Longitudinal National Data from Botswana

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BACKGROUND

- Cryptococcal meningitis (CM) remains a frequent opportunistic infection among individuals with advanced HIV disease, causing significant morbidity and mortality.
- CM incidence has fallen in high HIV-prevalence settings with narrowing of the ART treatment gap but persists at a stubbornly high incidence.
- Data presented at CROI 2024 showed cryptococcal meningitis incidence in Botswana has declined from 15.0 cases/100,000 person-years in 2015 to 7.4 cases/100,000 person-years in 2022 (Fig 1).
- However few countries other than South Africa collect reliable data on CM and robust longitudinal data describing the impact of HIV programme interventions and changes in management of CM on mortality in the rest of Africa are lacking.

METHODS

- National mortality estimates from patients with CM in Botswana were described using 8 years of national meningitis surveillance data (2015-2022) from electronic health records.
- All laboratory records from CSF samples analysed in government healthcare facilities in Botswana were extracted from a central online repository. CM case frequency was enumerated using a case definition.
- Mortality data were manually extracted from the national registry in duplicate using national identification numbers with arbitration by a third reviewer in discrepant cases.
- Outcomes were stratified as short-term (2 weeks), medium-term (10 weeks), long-term (1 year) from lumbar puncture date, and analysed by calendar year.
- Repeat presentation and cases without a national identification number were excluded.

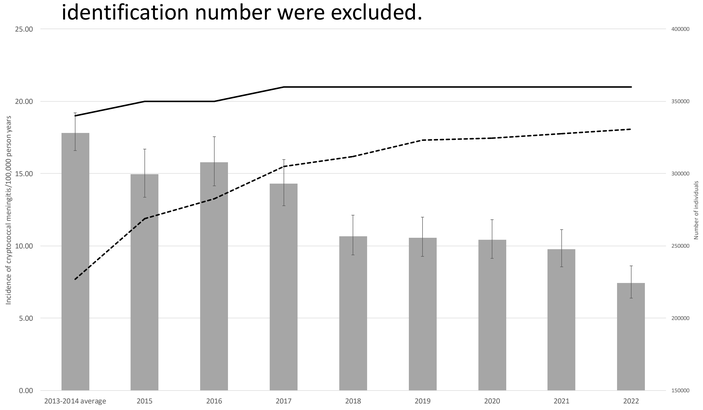


Figure 1 Incidence of cryptococcal meningitis in Botswana/100,000 person-years of observation from 2013-2022 (bar chart) with 95% confidence intervals UNAIDS estimate of total numbers of people with HIV (continuous line) and number of people receiving antiretroviral therapy (dotted line) – *presented at CROI 2024*

Despite excellent ART coverage and a decline in the incidence of cryptococcal meningitis, mortality in patients diagnosed with cryptococcal meningitis in Botswana remains high with no evidence of decline in 8 years of observation

Improved access to effective antifungals is essential to reduce mortality from cryptococcal meningitis

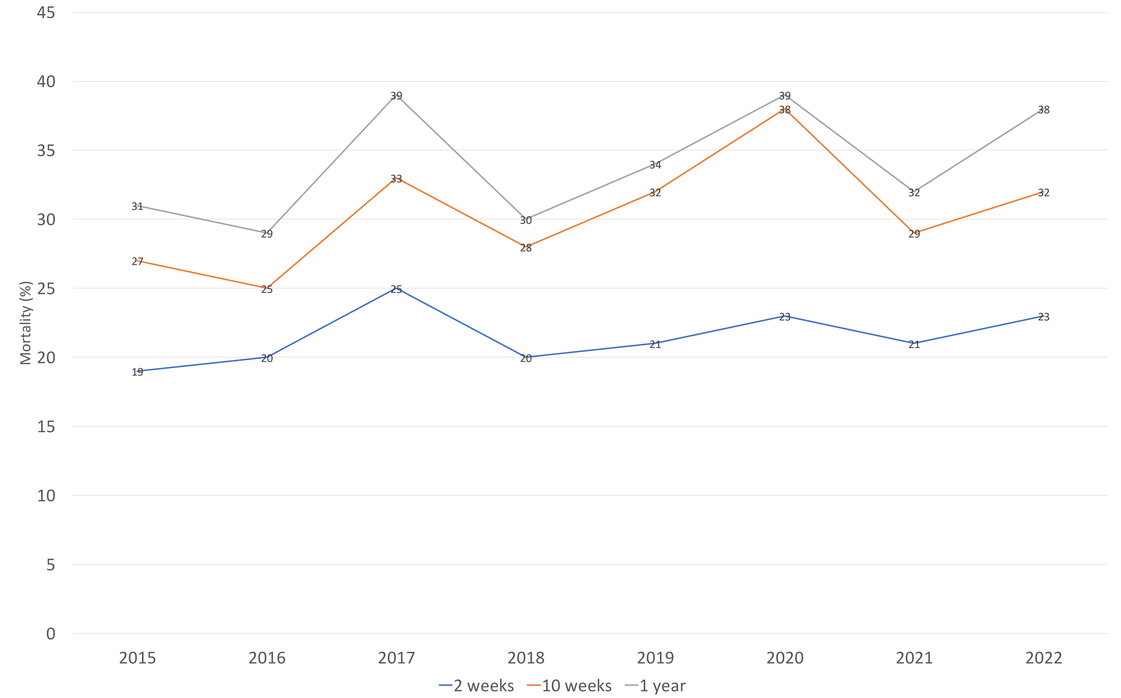


Figure 2 *Short-term (2-weeks), medium-term (10-weeks) and long-term (1 year) mortality in patients diagnosed with cryptococcal meningitis in Botswana between 2015 and 2022*

RESULTS

- Outcome data from 1259 first presentations of CM between 2015-2022 were analysed.
- Mortality at 2 weeks was 19% (95% CI 0.14-0.25, 37/193) in 2015 and 23% (95% CI 0.16-0.33, 24/103) in 2022, at 10 weeks 27% (95% CI 0.21-0.34, 52/193) and 32% (95% CI 0.23-0.42, 33/103) and at 1 year 32% (95% CI 0.25-0.38, 60/193) and 38% (95% CI 0.28-0.48, 39/103), respectively, with no clear temporal trend (Fig 2).
- Early mortality was significantly higher in older patients and those with positive CSF India ink, or lower CSF protein, glucose, or white cell count (Table 1).
- Early mortality was higher in district or primary hospitals (21.5%, 165/767) compared to referral hospitals (19.8%, 111/561), OR 1.6 (CI 1.3-1.9, p<0.01).

	Survived	Died	p-value
Age, median (IQR)	39.3 (33.9-45.6)	40.2 (34.3-46.9)	<0.01
Male sex, % (n)	79.3% (682)	20.7% (178)	<0.01
CD4, median (IQR)	54 (25-145)	41.5 (22-127)	<0.01
CSF glucose, median (IQR)	2.4 (1.6-3)	2.2 (1.0-3.1)	<0.01
CSF protein, median (IQR)	0.9 (0.5-1.5)	0.8 (0.5-1.5)	<0.01
CSF WCC, median (IQR)	4 (2-32)	2 (2-30)	<0.01
Positive CSF India ink, % (n)	18.2 (47)	22.8 (239)	<0.01
CSF culture positive for Cryptococcus sp.	14.7 (17)	23.6 (164)	<0.01

Table 1: Factors associated with short-term mortality in patients diagnosed with cryptococcal meningitis

CONCLUSIONS

- Mortality from CM in Botswana remains high and has not decreased in 8 years of observation despite narrowing of the ART treatment gap and improved diagnosis and management strategies.
- Increased mortality was observed in 2020, likely either directly attributable to COVID-19 or indirectly from disruptions to healthcare services.
- Treatment for CM has been simplified in updated WHO guidelines but access to effective antifungals including flucytosine in resource-limited settings remains restricted and must be addressed to reduce mortality.

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