Cryptococcal Meningitis as an Indicator for Monitoring HIV Treatment Program Success in Botswana

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BACKGROUND

- Cryptococcal meningitis (CM) remains a frequent opportunistic infection among individuals living with advanced HIV disease (AHD) in much of Africa.
- Despite widespread expansion of ART programmes including the introduction of universal treatment, modelled estimates indicate that the incidence of CM has not substantially decreased between 2014 and 2020, suggesting that the prevalence of AHD remains high in the region.
- Monitoring and understanding of mortality from AHD forms an important part of HIV programming but mortality data is often lacking and many indicators of AHD are either inaccessible due to cost or infrastructure, insensitive or used on predominantly outpatient populations making data collection more difficult.
- CM incidence could provide a useful indicator for monitoring AHD rates and HIV program success, especially in the context of declining access to CD4 testing as most patients present to healthcare facilities with a well-defined clinical syndrome, and diagnosis can be made using low-cost and highly accurate rapid diagnostic tests.

METHODS

- We analysed 8 years of national meningitis surveillance data (2015-2022) captured from electronic health records in Botswana. All laboratory records from cerebrospinal fluid samples analysed within government healthcare facilities in Botswana were extracted from a central online repository.
- Adjustments for missing data were made based on triangulation for underestimates using comprehensive prospective datasets.
- CM case frequency was enumerated using a case definition and incidence was calculated using national census data.

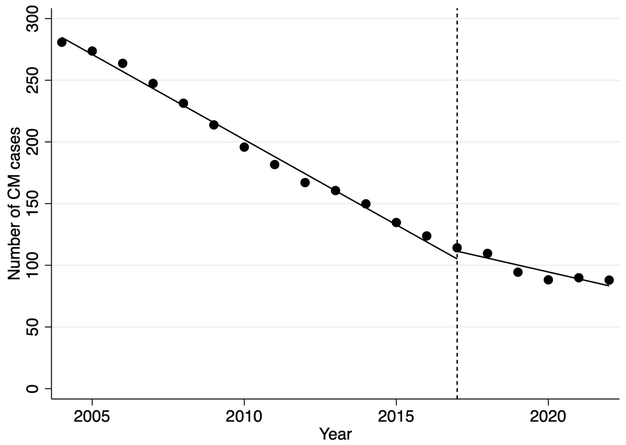

Figure 1 Frequency of cryptococcal meningitis cases at the 2 national referral between 2004 and 2023 in Botswana. Interrupted time series analysis used to generate predicted trends in cryptococcal meningitis cases pre- and post-introduction of universal treatment

Cryptococcal meningitis incidence in Botswana has declined from 15.0 (95% CI 13.4-16.7) cases/100,000 person-years in 2015 to 7.4 (95% CI 6.4-8.6) cases/100,000 person-years in 2022 with narrowing of the ART treatment gap but persists at a stubbornly high incidence

Most cases (86.3%) are now diagnosed through the cheap and easy-to-use cryptococcal antigen (CrAg) test highlighting the potential of using cryptococcal meningitis as key metric of HIV programme success

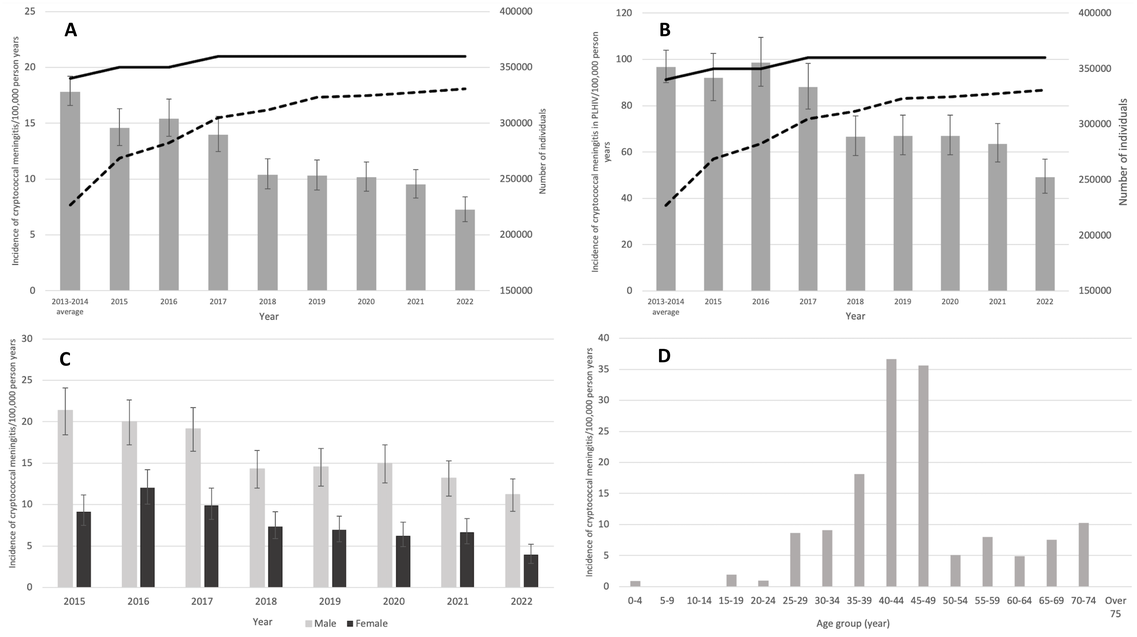

Figure 2A Incidence of cryptococcal meningitis in Botswana/100,000 person-years of observation from 2013-2022 (bar chart) with 95% confidence intervals UNAIDS estimate of total numbers of people with HIV (continuous line) and number of people receiving antiretroviral therapy (dotted line). **Figure 2B** Incidence of cryptococcal meningitis/100,000 person-years of observation in people living with HIV. **Figure 2C** Incidence of cryptococcal meningitis/100,000 person-years of observation by sex between 2015-2022 with 95% confidence intervals. **Figure 2D** Incidence of cryptococcal meningitis/100,000 person-years of observation by age category in 2022.

RESULTS

- A total of 1,744 episodes of CM were identified.
- The estimated national incidence of CM in Botswana approximately halved between 2015 and 2022, from 15.0 cases/100,000 person years (PYO) (95% CI 13.5-16.7 cases/100,00) to 7.43 cases/100,000 PYO (95% CI 6.4-8.6 cases/100,000).
- Among people living with HIV, the incidence of CM decreased from 92.0 cases/100,000 PYO (95% CI 82.2-102.6 cases/100,000 PYO) to 49.1 cases/100,000 PYO (95% CI 42.2-57.0 cases/100,000 PYO) between 2015 and 2022.
- There was no clear increase in the rate of decline following the introduction of universal treatment in 2016.
- The highest incidence was observed in men and individuals aged 40-44.
- The proportion of cases diagnosed through rapid cryptococcal antigen (CrAg) testing increased during the study period from 35.5% to 86.3%.

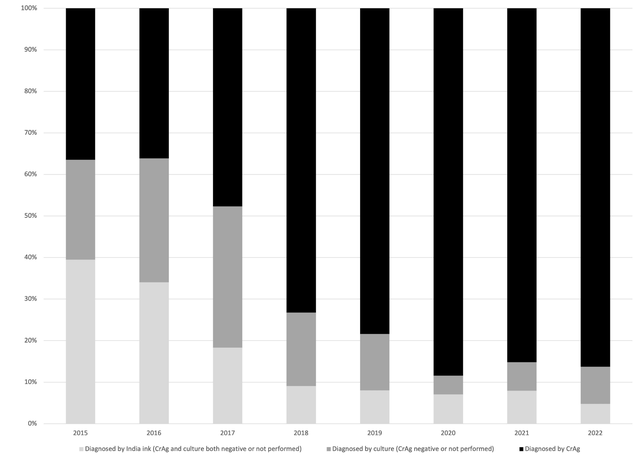

Figure 3: Yearly variation in cryptococcal meningitis diagnoses made through different diagnostic modalities. Group definitions: Diagnosed by CrAg – Positive CSF CrAg. India ink testing and culture positivity not accounted for. Diagnosed by culture – Positive CSF culture for Cryptococcus neoformans. CSF CrAg testing either negative or not performed. India ink testing not accounted for. Diagnosed by India ink – Positive CSF India ink stain. CSF CrAg and culture both negative or not performed.

CONCLUSIONS

- CM incidence has decreased with expanded ART treatment but persists at a relatively high rate despite excellent reported ART coverage.
- Most cases are now diagnosed through the rapid CrAg lateral flow assay highlighting the potential of using CM as key indicator for programme success in the Treat All era.

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