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The burden and epidemiology of HIV-associated cryptococcal meningitis and culture-confirmed cryptococcosis in South Africa, 2018–2023

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Summary

Cryptococcosis is a life-threatening opportunistic fungal infection, affecting many people living with HIV in South Africa. We analysed national laboratory-based surveillance data from 2018 to 2023 to assess the incidence, patient demographics, and factors associated with in-hospital mortality of HIV-associated cryptococcosis. We conducted a cross-sectional analysis of data from the GERMS-SA surveillance programme, calculating annual, provincial, age-specific, and sex-specific incidence risks. A random effects multivariable logistic regression model was used to explore factors associated with in-hospital mortality, including clinical characteristics and period of diagnosis relative to the COVID-19 pandemic. A total of 29 601 incident cases of cryptococcosis were detected (excluding cases of antigenaemia), with cryptococcal meningitis accounting for 95% of the cases. During the study period, the national incidence risk declined from 82 to 52 cases per 100 000 persons with HIV, with a steady decline observed in most provinces, except the Western Cape and Northern Cape. The highest incidence risk was among males aged 25–49 years. The overall crude in-hospital mortality was 37%, and factors independently associated with increased mortality included a CD4 cell count of <50 cells/mm^3, altered mental status, concurrent tuberculosis treatment, receiving antifungal induction therapy without flucytosine, and diagnosis during the COVID-19 pandemic. The burden of cryptococcal disease in South Africa declined during the study period, possibly owing to under-detection of cases, yet the incidence remained high, particularly among males, and mortality was persistently high. Sustained efforts to prevent advanced HIV disease, rapidly diagnose early cryptococcal disease, expand access to essential antifungals, and address sex-specific vulnerabilities are crucial to further reduce the disease burden and improve survival outcomes.

Introduction

Cryptococcosis, a life-threatening opportunistic fungal infection caused by *Cryptococcus neoformans* or *C. gattii*, is a major global health threat disproportionately affecting adults living with HIV.[1,2] HIV-associated cryptococcal disease can manifest as pneumonia, fungaemia, cryptococcal meningitis (CM), or disseminated culture-positive disease affecting multiple organs. Cryptococcal antigenaemia is a precursor to meningitis or disseminated disease. In 2020, an estimated 152 000 people developed CM globally, and the disease accounted for 19% of all AIDS-related deaths.[2] The majority of cases and associated deaths occur in low- and middle-income countries, with Africa bearing a particularly heavy burden, accounting for 82 000 CM cases and 71 000 cryptococcal-related deaths in 2020 alone.[2]

South Africa has the world's largest population living with HIV, with an estimated 7.5 million individuals aged 15 years and older in 2023.[3] Despite a significant expansion of antiretroviral therapy (ART) coverage, with 5.8 million people on treatment in 2023, the incidence of cryptococcosis remains persistently high. This is attributed to a large population with advanced HIV disease (AHD) who are either ART-naïve or have interrupted their treatment, engaging in care cyclically. A systematic review found that the prevalence of AHD was 43% (95% confidence interval [CI], 40.1%–46.8%) among ART-naïve patients and 58% (95% CI, 55.7%–61.5%) among ART-experienced patients.[4] As a result, the

incidence of cryptococcosis remains high, with >4 000 cases reported in South Africa in 2023.[1,5] The mortality rate for cryptococcosis among persons with HIV is also high, reaching up to 61% in routine care in low-income countries.[1] In 2023, approximately 38% of hospitalised patients with cryptococcosis in South Africa died.[5]

In 2016, South Africa implemented a national reflex cryptococcal antigen (CrAg) screening programme in which blood CrAg testing is automatically performed for all individuals with a CD4 count below 100 cells/mm^3. In August 2022, the Western Cape province revised the criteria for reflex testing, raising the threshold from <100 to ≤200 CD4 cells/mm^3.[6] While this programme was designed to detect cryptococcal disease (i.e., antigenaemia) at an earlier stage, followed by pre-emptive treatment with fluconazole to prevent CM, a recent evaluation showed that only 50% of patients with a new positive CrAg screening test actually received the recommended pre-emptive treatment.[3,7] In 2021, flucytosine, a critical antifungal agent required for the treatment of CM, was registered by the South African Health Products Regulatory Authority (SAHPRA). Inclusion of flucytosine in CM induction treatment regimens significantly reduced mortality in South Africa.[8] National guidelines were subsequently updated to recommend an induction treatment phase with amphotericin B, flucytosine, and fluconazole, followed by consolidation and maintenance phases with fluconazole. The impact of these updated guidelines on patient outcomes is not yet known.

Since 2005, GERMS-SA surveillance has monitored laboratory-confirmed cryptococcal disease nationally, with enhanced clinical surveillance at sentinel hospital sites. This report presents an analysis of HIV-associated CM and culture-confirmed cryptococcosis in South Africa over a six-year period using data from the GERMS-SA surveillance programme (https://www.nicd.ac.za/internal-publications/germs-sa/).

Methods

We conducted a cross-sectional analysis of the GERMS-SA nationwide laboratory-based surveillance for cryptococcosis in South Africa. To examine trends of cryptococcosis, we included all patients enrolled in GERMS-SA from 01 January 2018 to 31 December 2023. A demographic and clinical description of people with cryptococcosis was undertaken using information collected from laboratory records and through enhanced surveillance by nurse surveillance officers at 30 public-sector sentinel hospitals, using standardised case report forms. This analysis incorporated incident cases of laboratory-confirmed CM, fungaemia (a positive blood culture), and other culture-confirmed forms of cryptococcosis.

Definitions

A case of CM was defined as a patient with a cerebrospinal fluid (CSF) specimen with a positive India ink microscopy or positive CrAg test, or isolation of *Cryptococcus* spp. in culture during the study period. Fungaemia and other forms of cryptococcosis were defined as a positive culture for *Cryptococcus* spp. from blood or other anatomical sites, respectively. For the clinical description of the cases, we restricted the analysis to cases diagnosed at enhanced

surveillance sites with known HIV infection. A recurrent case of cryptococcosis was characterised as a positive cryptococcal test from any anatomical site occurring more than 30 days after the initial episode or a patient recorded as having a prior cryptococcosis episode without previous records in the current dataset. Although cases of isolated antigenaemia, defined as a positive CrAg test on blood without evidence of CM or culture-confirmed cryptococcosis, now contribute substantially to the burden of HIV-associated cryptococcal disease, we excluded these cases from this analysis for convenience.

Data analysis

Assuming that the vast majority of cases at a national level were HIV-associated, we calculated the annual province- and age-group-specific incidence risk as the number of incident cases of cryptococcosis divided by the number of people living with HIV and expressed incidence as cases per 100 000 persons living with HIV. We obtained population data from the Thembisa HIV modelling consortium (model version 4.8)[9] and calculated incidence risk for the age groups with available denominator data. For all incidence estimates, corresponding 95% CIs were calculated to determine the statistical significance of the changes (i.e., non-overlapping CIs). We described demographic and clinical characteristics of cases. For in-hospital mortality, we calculated 95% CIs for annual estimates for the surveillance period. We explored factors associated with in-hospital mortality at sentinel sites using a multivariable logistic regression. We included known risk factors, including age, sex, CD4 cell count, mental status, concurrent tuberculosis (TB) infection, and antifungal therapy (flucytosine-containing regimen vs. other). Additionally, we incorporated the period of diagnosis in relation to the COVID-19 pandemic, categorising this as pre-COVID-19 (01 January 2018–29 February 2020), during COVID-19 (01 March 2020–31 July 2022), and post-COVID-19 (01 August 2022–31 December 2023). To control for site differences, a random intercept for site was included in the model. Data analysis was performed using R software (version 4.5.1).

Results

Incident cases of cryptococcosis

We detected 31 701 cases of cryptococcosis, of which 29 601 were incident cases (Figure 1). Among incident cases, CM accounted for 95% (n=28 247), followed by fungaemia (4%; n=1 208). Overall, most incident cases were diagnosed in the KwaZulu-Natal (25%, n=7 383), Gauteng (23%, n=6 691), and Eastern Cape (16%, n=4 688) provinces. From 2018 to 2023, the proportion of cases in KwaZulu-Natal decreased (27% [1 601/6 002] to 22% [929/4 148]), while the proportion increased in the Western Cape (8% [458/6 002] to 13% [534/4 148], p<0.001) (Figure 2A). The median age was 37 years (interquartile range [IQR]: 31–44), and males accounted for the majority of cases (59%, 17 534/29 315). Female case-patients had a lower median age than males (36 years, IQR: 29–43 versus 38 years, IQR: 32–45, p<0.001). Among males and females, those aged 35–39 years and 30–34 years accounted for the most cases, respectively (Figure 3A).

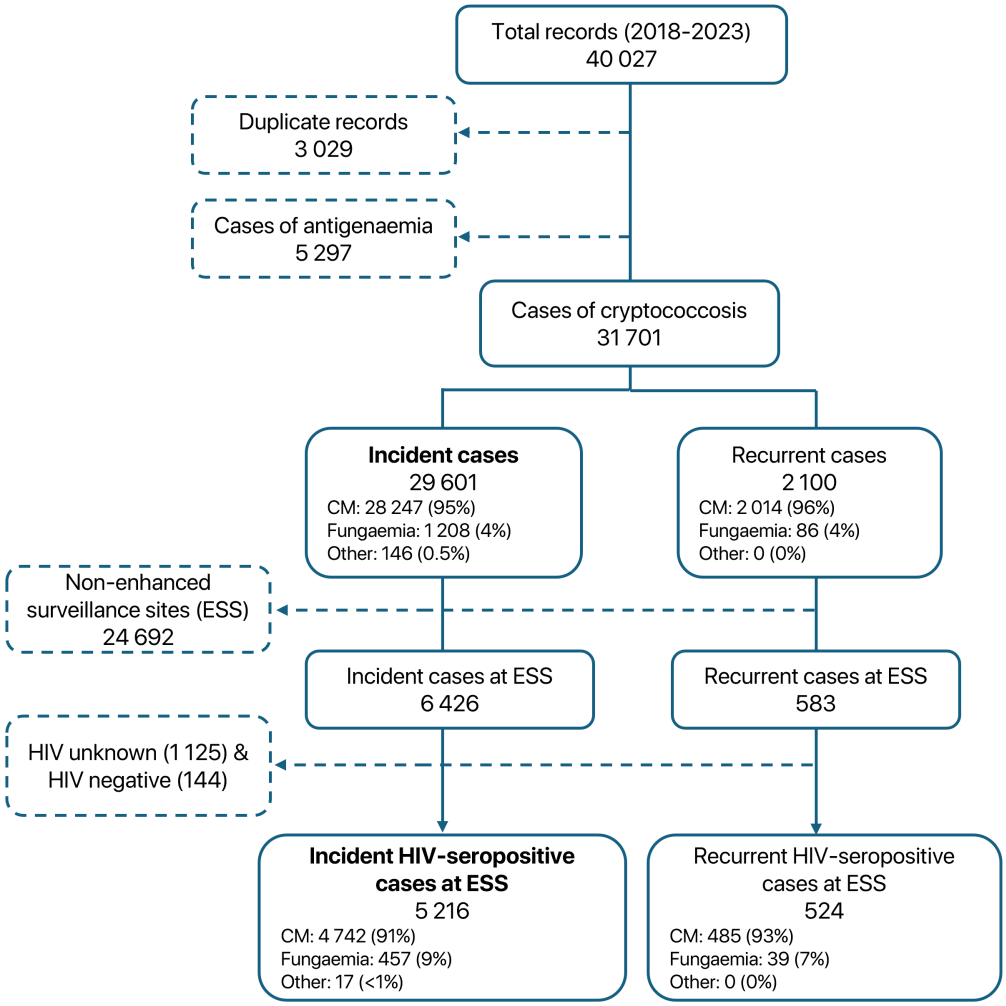

Figure 1. Incident and recurrent cases of cryptococcosis in South Africa, 2018–2023.

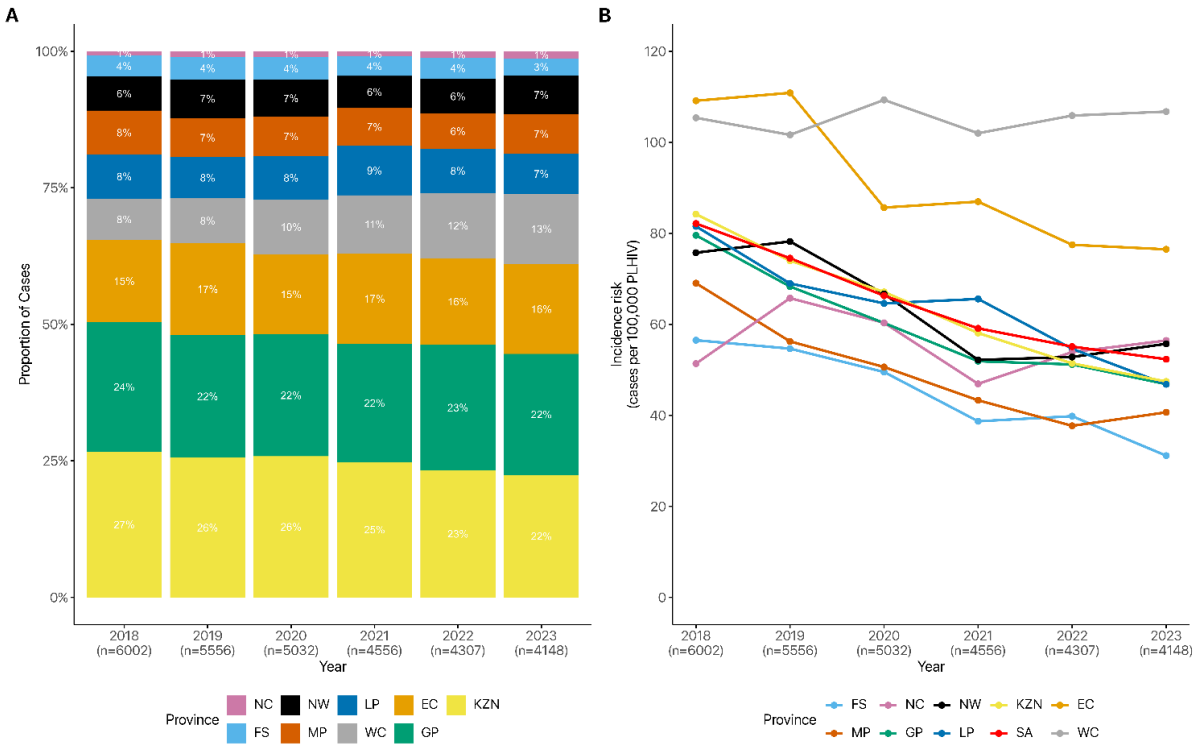

Figure 2. A) The annual provincial distribution of cases of cryptococcosis and B) the incidence risk of cryptococcosis among persons with HIV in South Africa, 2018–2023.

NC: Northern Cape, FS: Free State, NW: North West, MP: Mpumalanga, LP: Limpopo, WC: Western Cape, EC: Eastern Cape, GP: Gauteng, KZN: KwaZulu-Natal.

Incidence risk of cryptococcosis

The national incidence risk of cryptococcosis, excluding new cases of isolated antigenaemia, declined over time from 82 cases per 100 000 persons with HIV (95% CI: 80–84) in 2018 to 52 cases per 100 000 persons with HIV (95% CI: 50–53) in 2023 (Figure 2B). The Western Cape had the highest incidence risk, which remained steady over time (105 [95% CI: 95–115] to 107 [95% CI: 97–118] cases per 100 000 persons with HIV). The incidence risk in the Northern Cape also remained similar over the surveillance period (51 cases per 100 000 persons with HIV [95% CI: 37–69] in 2018 to 56 cases per 100 000 persons with HIV [95% CI: 42–73] in 2023). The Eastern Cape had the steepest decline in incidence risk, from 109 cases per 100 000 persons with HIV (95% CI: 102–117) in 2018 to 85 cases per 100 000 persons with HIV (95% CI: 79–92) in 2020. However, from 2020 to 2023, the incidence was steady: 85 [95% CI: 79-92] to 76 [95% CI: 70-82] cases per 100 000 persons with HIV. All other provinces experienced a steady decline in the incidence risk. Over the study period, the national average annual incidence risk for CM alone was 63 cases per 100,000 persons with HIV. This incidence risk decreased from 78 (95% CI: 76-81) in 2018 to 50 (95% CI: 48-51) in 2023.

Overall, the incidence risk of cryptococcosis was highest among persons with HIV aged 25–49 years, although it declined from 586 cases per 100 000 persons with HIV (95% CI: 569–604) in 2018 to 409 cases per 100 000 persons with HIV (95% CI: 394–424) in 2023 in this group (Figure 3B). While the incidence risk declined in all age groups, it remained stable in children aged <15 years-of-age (47 [95% CI: 39–56] in 2018 to 63 [95% CI: 52–76] in 2023). Among older age groups (i.e., ≥15 years of age), the cryptococcosis incidence risk was highest among males (range: 64–140 cases per 100 000 persons with HIV) compared to females (range: 21–50 cases per 100 000 persons with HIV). Males aged 25–49 years had the highest incidence risk of cryptococcosis (range: 91–140 cases per 100 000 persons with HIV), and those aged 15–24 years (range: 67–96 cases per 100 000 persons with HIV) and ≥50 years (range: 57–97 cases per 100 000 persons with HIV) had a similar incidence over the analysis period (Figure 3C). Across all older age groups and both sexes, there was a decline in incidence over time.

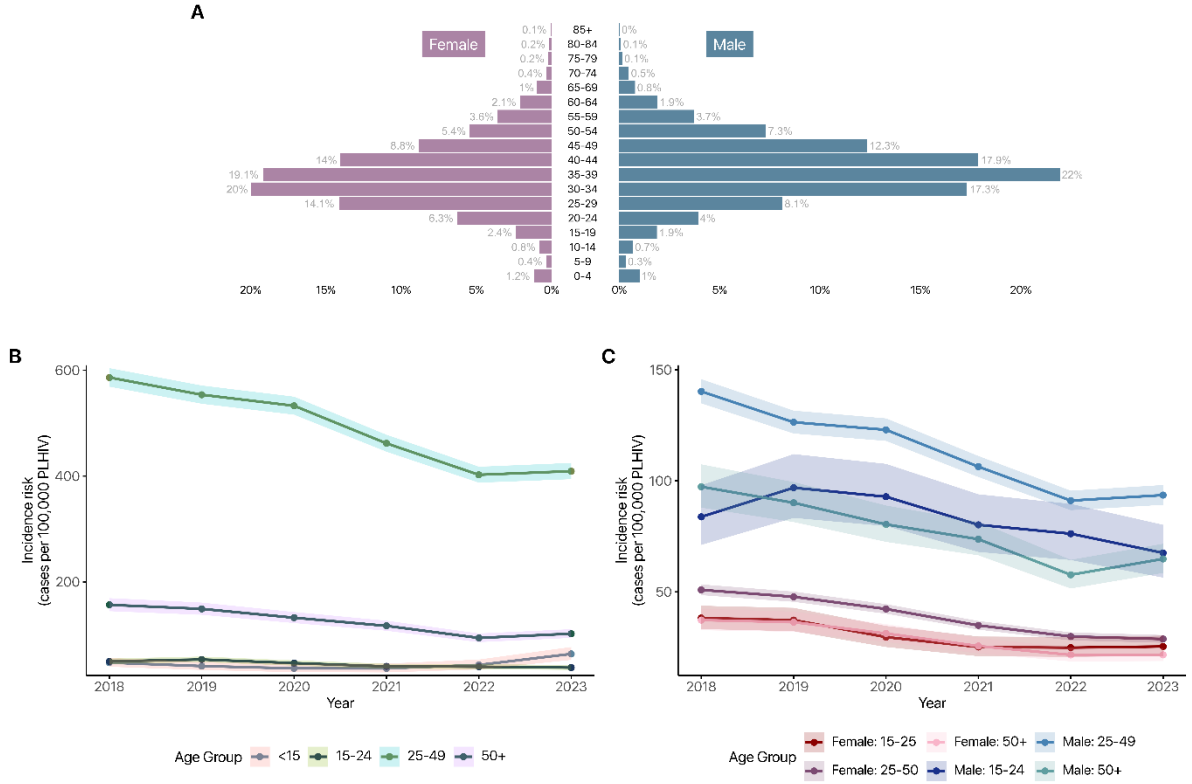

Figure 3. Cryptococcosis among persons with HIV in South Africa, 2018–2023. A) Age distribution among male and female incident cases of cryptococcosis; B) Incidence risk of cryptococcosis among persons with HIV by age group; and C) by age group and sex.

Note: Shading represents 95% confidence intervals.

Cases at enhanced surveillance sites

Of the incident cases of cryptococcosis, 6 426 (22%) were diagnosed at enhanced surveillance sites, and 98% (5 216/5 398) with known information were HIV-seropositive (Figure 1). Most people living with HIV were diagnosed with

meningitis (91%, n=4 742), followed by fungaemia (9%, n=457). The median age was 38 years (IQR: 32–44), and the proportion of males was 60% (3 128/5 206) (Table 1). Cases diagnosed in the Gauteng province accounted for the largest proportion (40%, 2 095/5 216) of cases at enhanced surveillance sites. Among patients with clinical information available, most were ART-experienced (61% [2 998/4 894]), had CD4 cell counts of <50 cells/mm^3 (64% [2 904/4 518]), and an HIV-1 viral load of >10 000 copies/mL (67% [2 184/4 769]). Among those with a CD4 cell count of <200 cells/mm^3 (4 213/4 518 [80%]), 2 911 had HIV-1 viral load information; 83% (n=2 416) and 17% (n=495) had a viral load of >400 copies/mL and <400 copies/mL, respectively. Overall, concurrent TB treatment was reported in 26% (1 307/4 937) (Table 1). Most cases received an amphotericin B-based regimen (46% [2 305/5 002]), and 10% (492/5 002) did not receive antifungal therapy. Among those who received more than one antifungal, 45% (1 855/4 160) received a flucytosine-containing regimen.

During the surveillance period, 2 100 recurrent episodes of cryptococcosis were detected (among 1 581 individuals); 583 were diagnosed at enhanced surveillance sites, and 524 of these episodes were known to occur among people living with HIV (Figure 1). The median age among these cases was 35 years (IQR: 29–40), and most were male (58% [306/524]). A majority had a CD4 cell count of <50 cells/mm3 (61% [298/485]), a viral load of >10 000 copies/mL (59% [232/395]) and were ART-experienced (88% [446/506]). For the recurrent episode, most received an antifungal regimen containing flucytosine (56%, [249/443]), and the in-hospital crude case fatality ratio was 28% (142/511).

Table 1. Characteristics of cases of HIV-associated cryptococcosis at enhanced surveillance sites, South Africa, 2018–2023.

Characteristics	N = 5 216
	n (% or IQR)
Median age (years)	38 (32–44)
Age group (years)	
<15	50 (1)
15-24	314 (6)
25-49	4 025 (79)
50+	683 (13)
Unknown	114
Sex	
Male	3 128 (60)
Female	2 078 (40%)
Unknown	10

Characteristics	N = 5 216
Province	
Gauteng	2 095 (40)
Eastern Cape	908 (17)
KwaZulu-Natal	836 (16)
North West	379 (7)
Mpumalanga	310 (6)
Western Cape	297 (6)
Limpopo	218 (4)
Free State	131 (3)
Northern Cape	42 (1)
ART experienced	
No	1 896 (39)
Yes	2 998 (61)
Unknown	322
CD4 count (cells/mm^3)	
<50	2 904 (64)
50-199	1 309 (29)
200-350	188 (4)
>350	117 (3)
Unknown	698
Viral load (log_{10} RNA copies/ml)	
<400	662 (20)
400-10 000	406 (12)
>10 000	2 184 (67)
Unknown	1964
WHO clinical stage	
1–3	219 (5)
4	4 494 (95)
Unknown	503
Concurrent TB	
No	3 630 (74)
Yes	1 307 (26)

Characteristics	N = 5 216
Unknown	279
Mental status	
Normal (GCS score of 15)	2 956 (65)
Altered (GCS score of <15)	1 582 (35)
Unknown	678
Antifungal therapy	
AMB + FLUC	2 305 (46)
5FC + FLUC + AMB	1 286 (26)
5FC + AMB	503 (10)
5FC + FLUC	66 (1)
Monotherapy*	350 (7)
No antifungals	429 (10)
Unknown	214
In-hospital outcome	
Survived	3 179 (63)
Died	1 878 (37)
Unknown	159

IQR: interquartile range, TB: Tuberculosis, GCS: Glasgow coma score, AMB: Amphotericin B, FLUC: Fluconazole, 5FC: Flucytosine, *Monotherapy included either fluconazole (n=262), amphotericin B (n=79), or flucytosine (n=9).

In-hospital mortality

The crude in-hospital mortality among cases of HIV-associated cryptococcosis was 37% (1 878/5 057). During the analysis period, the year-on-year mortality rate remained stable, ranging from 33% (95% CI: 31%–36%) in 2018 to 39% (95% CI: 35%–42%) in 2023 (Figure 4). In the multivariable logistic regression model including age and sex, a CD4 cell count of <50 cell/mm^3 (aOR 1.8 [95% CI: 1.27–2.66]), altered mental status (aOR 3.7 [95% CI: 3.13–4.41]), concurrent TB treatment (aOR 1.3 [95% CI: 1.08–1.56]), and antifungal therapy without flucytosine (aOR 1.8 [95% CI: 1.51–2.22]) were associated with mortality (Table 2). Cases diagnosed during the pre-COVID-19 period were 20% less likely to die (aOR 0.8 [95% CI: 0.6–0.98]) compared to those diagnosed during the pandemic. The in-hospital mortality rate of HIV-associated CM was 34% (1,574/4,597), with the lowest rate occurring in 2018 at 30% (95% CI: 28%–33%, 305/1,002) and the highest rate in 2021 at 40% (95% CI: 36%–44%, 241/608).

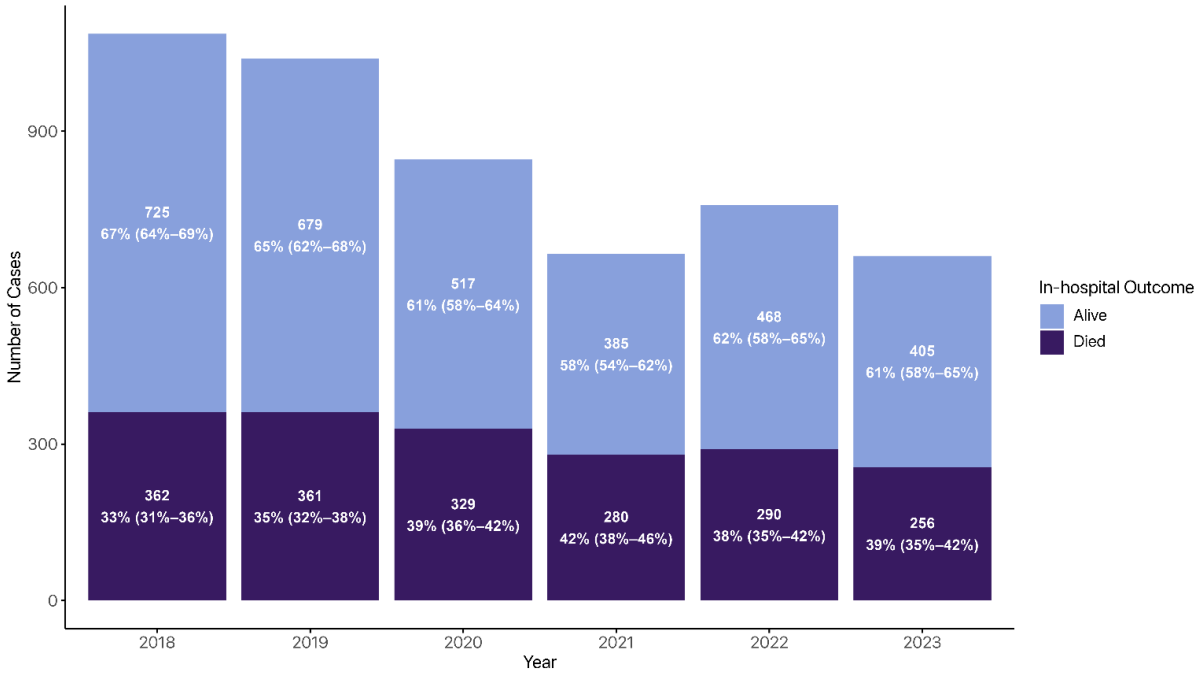

Figure 4. The number and in-hospital mortality among cases of HIV-associated cryptococcosis at enhanced surveillance sites, South Africa, 2018-2023.

Note: Alive includes patients who recovered or were discharged (including those who refused treatment) or transferred to another facility. Percentages in brackets represent the 95% confidence intervals.

Table 2. Factors associated with in-hospital mortality among cases of HIV-associated cryptococcosis at enhanced surveillance sites, South Africa, 2018–2023.

		Univariable			Multivariable	
Characteristic	**n**	**OR (95% CI)**	**p-value**	**n**	**aOR 95% CI**	**p-value**
Age group (years)						
<15	49	Ref		31	Ref	
15-24	310	1.1 (0.58-2.16)	0.800	216	1.0 (0.42-2.39)	0.999
25-49	3 911	1.3 (0.70- 2.39)	0.500	2 520	1.1 (0.46-2.38)	0.999
50+	655	2.0 (1.07-3.78)	0.035	411	1.9 (0.79-4.65)	0.400
Sex						
Female	2 017	Ref		1 265	Ref	
Male	3 030	1.1 (0.94-1.18)	0.400	1 913	1.0 (0.80-1.13)	0.600
Period of diagnosis						
During-COVID-19	1 790	Ref		1 103	Ref	
Pre-COVID-19	2 287	0.8 (0.69-0.89)	<0.001	1 419	0.8 (0.66-0.98)	0.030
Post-COVID-19	980	1.0 (0.84-1.16)	0.999	656	0.9 (0.75-1.17)	0.500
CD4 count (cells/mm^3)						
≥200	291	Ref		198	Ref	
50-199 (vs)	1 261	1.3 (0.95-1.68)	0.120	915	1.3 (0.85-1.85)	0.300
<50	2 829	1.7 (1.31-2.26)	<0.001	2 065	1.8 (1.27-2.66)	0.001
Mental status						
Normal	2 934	Ref		2 162	Ref	
Altered	1 547	3.7 (3.29-4.26)	<0.001	1 016	3.7 (3.13-4.41)	<0.001
Concurrent TB treatment						
No	3 587	Ref		2 286	Ref	
Yes	1 285	1.3 (1.15-1.50)	<0.001	892	1.3 (1.08-1.56)	0.006
Antifungal therapy						
Flucytosine regimen	1 825	Ref		1 449	Ref	
Other regimens*	2 285	1.4 (1.19-1.56)	<0.001	1 729	1.8 (1.51-2.22)	<0.001

OR: odds ratio, CI: confidence interval, aOR: Adjusted odds ratio, TB: Tuberculosis, *Other regimens include regimens without flucytosine and exclude monotherapy.

Discussion

Despite the expansion of the South African ART programme, cryptococcosis remains a major cause of morbidity and mortality among people living with HIV, contributing significantly to AIDS-related deaths. Our analysis revealed a significant 36% decline in the incidence of CM and culture-confirmed cryptococcosis in South Africa, aligning with global trends. However, this incidence remains markedly higher than in high-income countries such as Australia (15 per 100 000 persons with HIV in 1997) and the United States (7 cases per 100 000 in 2002), where ART has had a greater impact.[10,11] The high burden of cryptococcosis in African countries, for example, the comparable incidence of 92.9 cases of CM per 100 000 adult people with HIV (95% CI: 86.2-99.9) in Botswana (2013-2014), is largely driven by the persistently high prevalence of AHD.[12] An estimated 1.9 million people were affected by AHD in Africa between 2016 and 2021.[13] The persistence of AHD is a complex issue influenced by several factors, such as late HIV diagnosis, delayed ART initiation, poor retention in care and cyclical treatment interruptions, programmatic gaps in ART coverage and viral suppression, and other social determinants of health, such as level of knowledge and stigma.[4,13–15] Despite the overall decline in cryptococcosis incidence, the number of cases is still high, imposing a persistent burden on patients and the South African healthcare system.

The burden of disease was not uniform across the country. Despite having the lowest prevalence of HIV (7% vs. 12% nationally in 2022),[15] the Western Cape had the highest incidence of cryptococcosis, which remained elevated throughout the analysis period. Given that the Western Cape has a similar HIV population profile to other provinces, including rates of HIV status awareness and ART coverage, the reason for a different trend in this province is unclear.[15] Higher rates of diagnostic sample collection, such as CSF and blood cultures, along with a reflex CrAg testing threshold of ≤200 CD4 cells/mm^3 in this province, likely contributed to higher and potentially more accurate case detection rates.[6] During the COVID-19 pandemic, the Western Cape was the only province in the country that maintained similar CrAg test volumes compared to 2018, even showing a 15% increase in volumes in 2021.[16] In addition, people with AHD may have better access to health services in this province with a correspondingly greater chance of an opportunistic infection being diagnosed.

In contrast, data from most other provinces showed a steady decline of cryptococcosis. The decline across these provinces could be attributed to the effectiveness of public health initiatives such as the national CrAg reflex screening programme, which facilitates early detection and pre-emptive fluconazole treatment, preventing progression to CM and cryptococcosis.[7] But this seems unlikely since a recent national evaluation of the CrAg screening programme has shown that a large proportion of patients with antigenaemia are not appropriately followed up or treated.[7] In their systematic review and meta-analysis, Kitenge *et al*. reported a 2% annual decrease in the proportion of ART-naïve patients presenting with AHD, suggesting any improvement in access to HIV care and ART services has been modest.[4] The sharp incidence decline in the Eastern Cape in 2020 may have been due to a combination of factors related to the COVID-19 pandemic, including interruption in health services, changes in healthcare-seeking behaviour, and increased deaths during lockdowns and restrictions.

Despite a higher national HIV prevalence among females (16.4% compared to 8.8% in 2022), we found that males were disproportionately affected by cryptococcosis, with an incidence approximately three times that of females.[15] At sentinel sites, males also accounted for nearly two-thirds of hospitalised patients with cryptococcosis. This disparity has been documented in prior studies and is attributed to several factors. Men are more likely to present late for HIV care, delay ART initiation and, consequently, have higher rates of AHD.[13–15] These tendencies are often linked to a complex interplay of sociocultural factors, including traditional notions of masculinity, stigma, and various health system barriers.[13–15] Our findings emphasise the critical need for gender-specific research and service delivery models. Tailoring these approaches could help encourage earlier ART initiation and improve retention in care for men, ultimately preventing AHD and associated opportunistic infections such as cryptococcosis.

We found that most cryptococcosis cases occurred among ART-experienced individuals with severe immunosuppression (almost two-thirds with a CD4 count of <50 cells/mm³). Similar trends have been reported in South Africa, where an increasing proportion of AHD arises from treatment interruption or failure rather than being ART-naïve.[4] This suggests that programmatic priorities must go beyond early ART initiation to include robust strategies for retention in care, adherence support, and rapid re-engagement of those who interrupted care. Interestingly, we found a fifth of patients were virally suppressed, including those with AHD (i.e., CD4 count of <200 cells/mm³). This may reflect patients who have recently initiated or re-initiated ART and developed unmasking cryptococcal immune reconstitution inflammatory syndrome.[17] The shift to using viral loads over CD4 counts for routine HIV disease monitoring presents a challenge. Some patients who appear to be in good health based on a suppressed viral load may not receive adequate screening and treatment for cryptococcosis. Our results show that CD4 testing and CrAg screening remain crucial adjunct tools for managing ill patients with HIV. Furthermore, we found that more than a quarter of cases were on concurrent TB treatment, consistent with the high prevalence of TB-HIV co-infection in South Africa. These findings emphasise that people with cryptococcosis often require multiple diagnostic and management tools to ensure comprehensive care and prevent poor outcomes. We observed a substantial number of patients with recurrent, culture-confirmed cryptococcal disease, which contributes substantially to the overall disease burden. However, we found that mortality was lower among patients with recurrent disease compared to those with incident disease. This likely reflects the fact that these individuals survived their initial episode and, consequently, had a greater opportunity to receive subsequent therapeutic interventions. For example, a higher proportion of patients with recurrent disease were on ART at the time of their subsequent episode(s), and nearly two-thirds received flucytosine-containing regimens. These factors likely contributed to their improved survival outcomes.

We observed a persistently high crude in-hospital mortality among patients with HIV-associated cryptococcosis, with rates remaining stable year-on-year. Several factors were independently associated with mortality. Severe immunosuppression (CD4 <50 cells/mm³) nearly doubled the risk of death, reinforcing the critical importance of early HIV diagnosis and ART initiation to prevent AHD. Altered mental status, which reflects severe CM with a high cryptococcal burden in CSF, was the strongest predictor (aOR 3.7). This is an established association.[8] Notably,

patients receiving antifungal therapy without flucytosine had an 80% higher risk of death compared to those receiving flucytosine-containing regimens. This supports existing evidence from the Advancing Cryptococcal Meningitis Treatment for Africa (ACTA) trial and observational studies demonstrating the survival benefit of flucytosine-containing induction therapy.[8,19] Despite flucytosine registration with SAHPRA and inclusion in the South African National Adult Hospital Standard Treatment Guidelines and Essential Medicines List, frequent stock-outs of flucytosine remain a major barrier to optimal care.[20] Interestingly, mortality risk was lower in the pre-COVID-19 period compared to the pandemic period, suggesting potential disruptions to routine HIV and cryptococcal disease care during the pandemic. Reduced access to diagnostic services, delayed presentation, and interruptions in supply chains for antifungal medicines may have contributed to this observed increase in mortality risk during and after COVID-19.[21]

Limitations

This analysis offers a cross-sectional view of cryptococcosis nationally but has limitations. Cryptococcal antigenaemia can persist for years following initial disease; we excluded all cases of antigenaemia from incidence estimates to prevent misclassification. But this resulted in the omission of new episodes of antigenaemia and thus yielded conservatively low disease burden estimates. Our incidence calculations used the number of people living with HIV as the denominator, which may slightly overestimate the burden since a small proportion of cryptococcosis cases occur in HIV-negative individuals. Mortality estimates were derived from enhanced surveillance sites, primarily higher-tier hospitals, where patients may present with more advanced cryptococcal disease and treatment practices may differ from those in lower-tier facilities. This could lead to an underestimation of mortality if access to antifungals and critical care was more limited at lower-tier hospitals, or an overestimation if patients at higher-tier hospitals were more severely ill. Additionally, our mortality data lacked information on other key prognostic factors, such as intracranial pressure and CSF cell count, which could have impacted our risk estimates. Finally, the GERMS-SA enhanced surveillance data only includes the public health sector. While the private health sector contributes only a modest portion to the overall disease burden, our findings may not fully capture the complete picture of cryptococcosis across South Africa.

Conclusion

The burden of cryptococcal disease declined over the six-year period, reflecting either under-detection of cases related to health systems issues or a potential impact of strengthened public health interventions. Men continue to be disproportionately affected, highlighting the need for targeted, gender-responsive prevention strategies. Mortality remained unacceptably high despite the availability of the life-saving flucytosine as well as other antifungals; these ongoing gaps in timely diagnosis, treatment initiation, and access to optimal regimens need to be addressed. Sustained efforts to enhance early detection of antigenaemia and pre-emptive treatment, expand access to essential antifungals, and address gender-specific vulnerabilities are critical for further reducing the burden and improving survival outcomes.

Recommendations

- The National Department of Health (NDoH) should evaluate gender-specific components (e.g., evening/weekend community-based clinics) within its differentiated service delivery model, designed to increase earlier HIV diagnosis and improve ART engagement/retention for men. Pilot studies should be launched within 12 months.
- NDoH and provincial departments of health should achieve and maintain high stock availability of essential antifungal agents, including flucytosine, amphotericin B, and fluconazole, at the national and provincial depot level to prevent stock-outs. The NDoH should set up a national dashboard to track essential commodities for AHD care by 2026.
- Healthcare facilities and clinicians should ensure all eligible patients receive the recommended induction therapy, increasing the proportion of patients receiving flucytosine-containing induction regimens by 50% within 12 months.
- Provincial and district departments of health should establish provincial or district-level teams to audit and trace positive CrAg results from the national laboratory system to improve full follow-up and pre-emptive treatment for all individuals who test newly positive for cryptococcal antigenaemia. These teams should implement a tracing system and begin quarterly reporting in all provinces within 12 months of being established.
- The NDoH should update the national HIV management guidelines to explicitly mandate CD4 count and reflex CrAg screening for all patients with AHD indicators (e.g., WHO clinical stage 3/4, opportunistic infection diagnosis including TB, or hospitalisation), even if viral suppression is documented.
- Provincial and district departments of health should implement a patient health literacy and empowerment programme across clinics to increase patient knowledge of AHD prevention, CrAg screening, CM, and lifelong ART adherence. The pilot curriculum development and training should be done within 18 months, and the first round of programme implementation and evaluation within the next 24 months.

Ethical considerations

The University of the Witwatersrand Human Research Ethics Committee (Medical) granted ethical clearance to the National Institute for Communicable Diseases (M210752) and the GERMS-SA national programme (M230985) to conduct essential communicable disease surveillance.

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Conflicts of interest

None to declare.

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