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South Africa

Epidemiology of cryptococcal disease in the Eastern, Northern, and Western Cape provinces of South Africa, 2022–2024

Tiisetso Lebaka[1*], Susan Meiring[1*], Mokupi Manaka[1], Vindana Chibabhai[2,3,4], Caroline Maluleka[2,3], Amanda Shilubane[2], Liliwe Shuping[3], Rudzani Mashau[3], Denise Kyazze[5,6], Loyiso Mnqokoyi[7], Elizabeth Prentice[8], Uafulufhedzea Ndou[9], Kessendri Reddy[10], Sipho Dlamini[11], Arifa Parker[12], Nelesh P. Govender[2,3], Vanessa Quan[1*] for GERMS-SA

[1]Division of Public Health Surveillance and Response, National Institute for Communicable Diseases, a division of National Health Laboratory Service, Johannesburg, South Africa

[2]Centre for Healthcare-Associated Infections, Antimicrobial Resistance and Mycoses, National Institute for Communicable Diseases, a division of National Health Laboratory Service, Johannesburg, South Africa

[3]Wits Mycology Division, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[4]Division of Clinical Microbiology and Infectious Diseases, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[5]Livingstone Tertiary Hospital, Infectious Diseases Unit, Department of Internal Medicine, Gqeberha, South Africa

[6]Nelson Mandela University Medical School, Gqeberha, South Africa

[7]National Health Laboratory Service, Port Elizabeth, South Africa

[8]University of Cape Town and Groote Schuur Hospital, National Health Laboratory Service, Cape Town, South Africa

[9]Tygerberg Microbiology Laboratory, National Health Laboratory Service, Cape Town, South Africa

[10]Division of Medical Microbiology, Faculty of Medicine and Health Sciences, Stellenbosch University and National Health Laboratory Service, Tygerberg, Cape Town, South Africa

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[11]Division of Infectious Diseases and HIV Medicine, Department of Medicine, Faculty of Health Sciences, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa
[12]Unit for Infection Prevention and Control and Division of Infectious Diseases, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa

*Corresponding author

Summary

Cryptococcal disease remains a major opportunistic infection among people living with HIV in South Africa, contributing substantially to morbidity and mortality despite expansion of antiretroviral therapy (ART) coverage. Using data from the GERMS-SA laboratory-based surveillance programme, we describe the demographics, clinical characteristics, antifungal treatment, and outcomes of patients with laboratory-confirmed cryptococcal disease in the Eastern, Northern, and Western Cape provinces of South Africa between 01 January 2022 and 31 December 2024. All laboratory-confirmed cases reported through the National Health Laboratory Service and private laboratories were included, and additional data (including treatment and outcome) were collected using standardised case report forms at enhanced surveillance sites. Among 3 656 laboratory-confirmed cases, 1 967 were adults aged 30–44 years (54%), and 58% were male (1 149/1 967). The majority of patients were living with HIV, with a median (interquartile range) CD4 count of 32 (13–63) cells/µL. Cerebrospinal fluid specimens accounted for 94% (522/554) of diagnostic specimens, consistent with cryptococcal meningitis as the primary clinical presentation. Across the three provinces, the overall in-hospital case fatality rate was 30% (139/461), with consistently lower case fatality (25% (95/374)) among patients treated with flucytosine-containing regimens compared with non-flucytosine regimens (51% (44/87), p<0.001). These findings highlight the survival benefit associated with flucytosine-based therapy. Strengthening routine HIV screening, ART retention, and consistent flucytosine availability across facilities is essential to improving outcomes in cryptococcal disease. Continued surveillance is important to inform policy and ensure equitable access to optimal antifungal treatment, including flucytosine access, across South Africa's provinces.

Introduction

Cryptococcal disease remains a leading cause of illness and death among people living with HIV, particularly in Africa. Before widespread access to antiretroviral therapy (ART), cryptococcal meningitis (CM) was amongst the most common and severe opportunistic infections. Although its prominence has declined with ART expansion, the disease still causes an estimated 180 000 deaths each year, largely among individuals with advanced HIV disease (AHD), driven principally by the pathogenic species complexes *Cryptococcus neoformans* and *Cryptococcus*

gattii.[1,2] In South Africa, late HIV diagnosis, interruptions in ART, and gaps in linkage to care continue to sustain the substantial burden of AHD and hence CM.[3,4] Recent GERMS-SA surveillance estimated a national incidence risk of approximately 54 cases per 100 000 people living with HIV in 2023, decreasing to about 48 per 100 000 in 2024.[5,6]

The World Health Organization and many national HIV programmes, including South Africa's AHD guidance, recommend early cryptococcal antigen (CrAg) screening and timely antifungal treatment for antigenaemia or CM as critical components of AHD management.[7,8,9] However, implementation remains uneven. Many primary care facilities serve geographically dispersed communities, making patient follow-up difficult, and persistent gaps in CrAg coverage, ART linkage, and access to key antifungal medicines such as flucytosine, limit programme impact.[9,10,11]

Despite the vulnerability of affected patients and the fact that CM progression is at least partly preventable through early screening and treatment, recent provincial trends in epidemiology, including treatment and outcomes, remain poorly characterised. Updated evidence is essential for informing targeted and equitable public-health responses.

The objective of this study was to describe the epidemiology, including clinical characteristics, antifungal treatment, and outcomes, of laboratory-confirmed cryptococcal disease reported through the GERMS-SA surveillance programme in the Eastern, Northern, and Western Cape provinces of South Africa between 01 January 2022 and 31 December 2024.

Methods

Study design and setting

This was a descriptive study using data from the GERMS-SA national laboratory-based surveillance programme, which monitors laboratory-confirmed cases of cryptococcosis reported by both public and private clinical microbiology laboratories across South Africa.[5,6] This analysis included all laboratory-confirmed cases of cryptococcosis identified between 01 January 2022 and 31 December 2024 in the Eastern Cape (EC), Northern Cape (NC), and Western Cape (WC) provinces, and was not intended to compare provinces directly but rather to provide a provincial overview.

Inclusion and exclusion criteria

The study population comprised all individuals with confirmed cryptococcal disease diagnosed in the three provinces during the study period. Inclusion criteria for an incident case of cryptococcosis were defined by a positive cerebrospinal fluid (CSF) India ink test, a positive CSF CrAg test or culture of *Cryptococcus* species from any specimen. Duplicate episodes, defined as any positive laboratory sample within 30 days, were excluded. Cases of isolated cryptococcal antigenaemia (the presence of CrAg in the blood) were not included.

Data sources and collection

Laboratory results were obtained from the National Health Laboratory Service (NHLS) Corporate Data Warehouse (CDW) and private pathology reports, and included specimen type and diagnostic tests performed. As part of the GERMS-SA laboratory-based surveillance programme, participating public and private laboratories submit isolates that meet the cryptococcosis case definition to the National Institute for Communicable Diseases (NICD), a division of the NHLS, for confirmation and characterisation.

Enhanced surveillance sites (ESS) are selected referral hospitals where additional clinical data are routinely collected alongside laboratory confirmation. During the study period, ESS included three hospitals in the EC (Port Elizabeth National, Livingstone, and Dora Nginza Hospitals), one in the NC (Robert Mangaliso Sobukwe Hospital), and three in the WC (Red Cross War Memorial Children's Hospital, Groote Schuur Hospital, and Tygerberg Hospital). At these sites, trained surveillance nurses collected demographic, clinical, and treatment information using standardised case report forms (CRFs). Data from non-enhanced sentinel sites were limited to laboratory-confirmed cases without corresponding clinical details.

All data were merged into a GERMS-SA Microsoft Access database for validation and cleaning. The database was checked for recurrent episodes, duplicates, inconsistent coding, and missing values before analysis.

Data management and analysis

Data cleaning and management were conducted using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) and R statistical software (version 4.5.1; R Foundation for Statistical Computing, Vienna, Austria).

Both descriptive and inferential statistics were used. Descriptive analyses summarised categorical variables as frequencies and percentages, and continuous variables as medians with interquartile ranges (IQRs). Inferential analyses included Fisher's exact test for categorical comparisons, with 95% confidence intervals and p-values reported where appropriate.

Incident cryptococcal cases were stratified by year, sex, and age category, and incidence risks were calculated using provincial population denominators derived from Statistics South Africa mid-year estimates[12] and the Thembisa model version 4.8.[13]

The in-hospital case fatality rate (CFR) was used as the main outcome measure, defined as the proportion of patients who died among those with known outcomes. Antifungal induction treatment was categorised as any regimen with flucytosine versus any regimen without flucytosine.

Results

Overview of reported cryptococcal disease cases

Between 01 January 2022 and 31 December 2024, GERMS-SA detected 3 656 laboratory-confirmed cases of cryptococcal disease across the EC, NC, and WC provinces. Of these, 664 (18%) cases were identified at ESS, where clinical information is routinely collected, while the remaining 2 992 (82%) cases were reported from non-ESS facilities where no clinical data is available (Figure 1).

Among ESS cases, 83% (554/664) had clinical information, while 110 cases (17%) had missing HIV status or incomplete forms. Data completeness varied by province, ranging from 63% in the NC to 85% in the EC and WC.

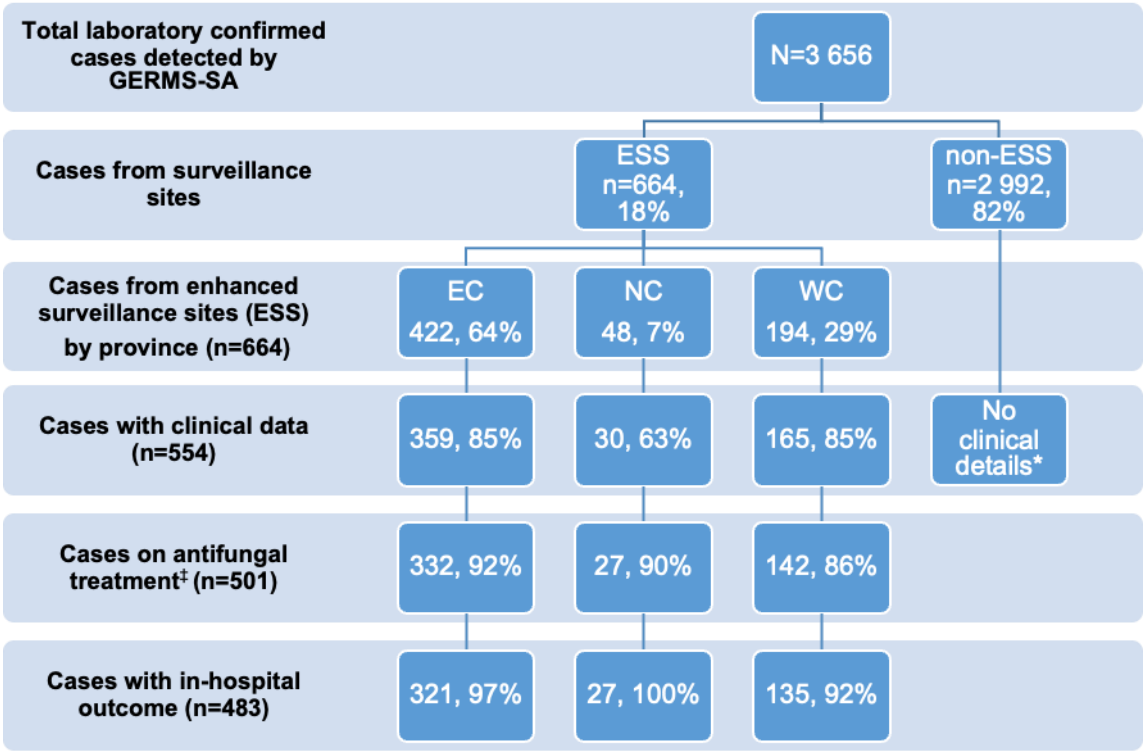


Figure 1. Laboratory-confirmed cryptococcosis cases on antifungal treatment with a known outcome. GERMS-SA, Eastern (EC), Northern (NC), and Western Cape (WC) provinces, South Africa, 2022–2024, n=3 656.

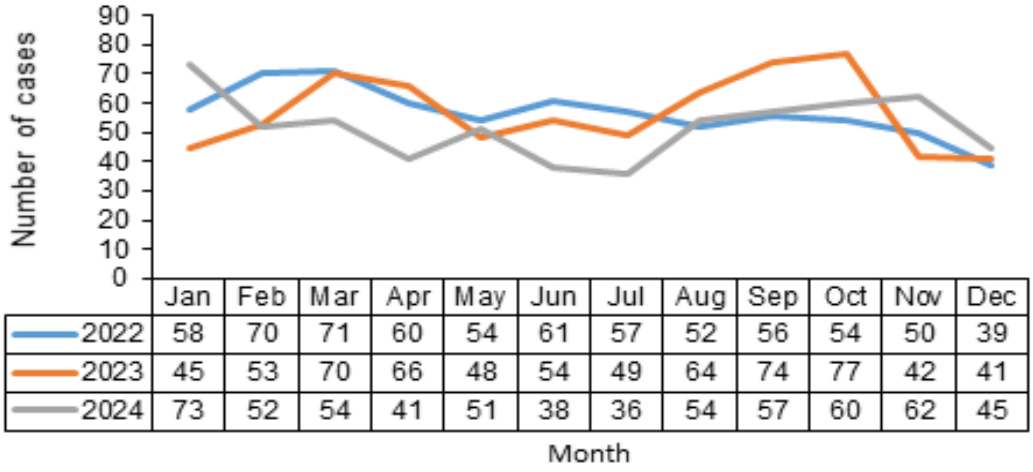
*No surveillance nurse on site; therefore, cases limited to laboratory-confirmed cases with limited clinical details from available medical records.

‡Antifungal treatment was analysed as regimens with or without flucytosine.

Incident cases of cryptococcosis

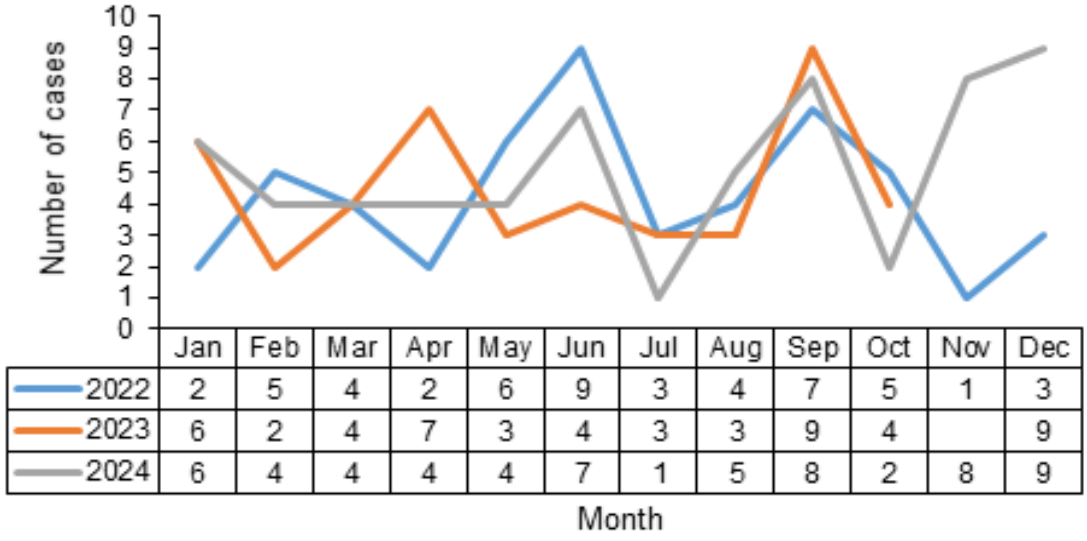
Across the three-year period we detected 3 656 cases of cryptococcosis, and monthly counts fluctuated without a clear seasonal pattern (Figures 2A–C). The EC consistently contributed the highest number of cases, with monthly

totals ranging from 39 to 73 (Figure 2A) and a slight decline in annual counts from 683 in 2023 to 623 in 2024 (Table 1). The WC showed a similar pattern, with monthly case counts between 29 and 61 (Figure 2C), stable totals in 2022 and 2023 (517 and 534 cases) and a decrease to 450 cases in 2024. The NC contributed the fewest cases, with one to nine cases per month (Figure 2B) and modest increases in annual totals from 51 in 2022 to 62 in 2024 (Table 1).



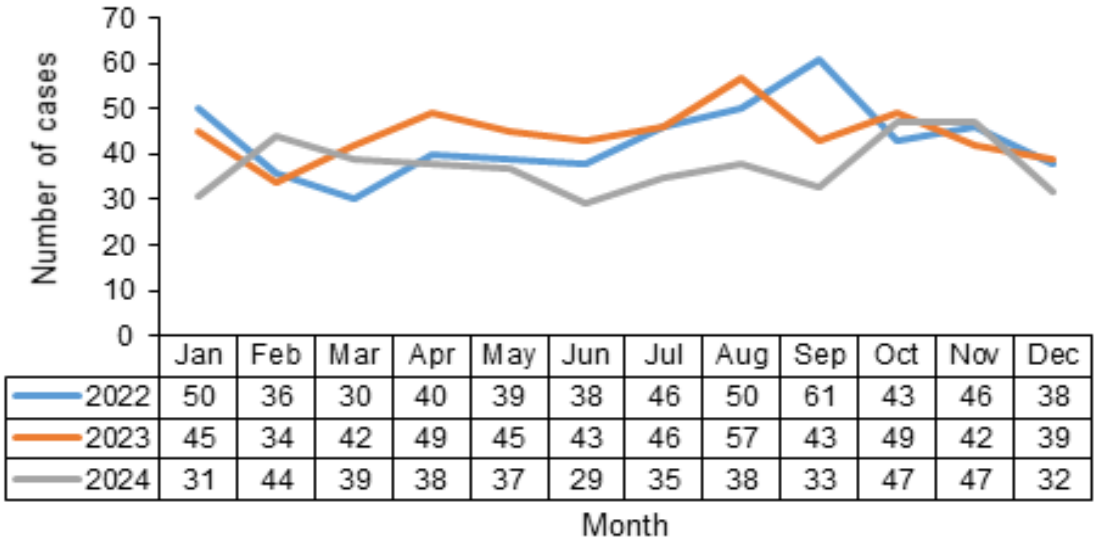
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
2022	58	70	71	60	54	61	57	52	56	54	50	39
2023	45	53	70	66	48	54	49	64	74	77	42	41
2024	73	52	54	41	51	38	36	54	57	60	62	45

Figure 2A. Monthly laboratory-confirmed cryptococcal disease cases reported from South Africa's Eastern Cape province, GERMS-SA, 2022–2024 (N=1 988).



	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
2022	2	5	4	2	6	9	3	4	7	5	1	3
2023	6	2	4	7	3	4	3	3	9	4		9
2024	6	4	4	4	4	7	1	5	8	2	8	9

Figure 2B. Monthly laboratory-confirmed cryptococcal disease cases reported from South Africa's Northern Cape province, GERMS-SA, 2022–2024 (N = 167).



	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
2022	50	36	30	40	39	38	46	50	61	43	46	38
2023	45	34	42	49	45	43	46	57	43	49	42	39
2024	31	44	39	38	37	29	35	38	33	47	47	32

Figure 2C. Monthly laboratory-confirmed cryptococcal disease cases reported from South Africa's Western Cape province, GERMS-SA, 2022–2024 (N = 1 501).

Incidence risk of cryptococcosis

The WC province had the highest incidence risk throughout the study period, with 106 cases per 100 000 persons with HIV in 2022, which declined in 2024 (88 cases per 100 000 persons with HIV). In contrast, the EC maintained a high but stable incidence (between 69 and 77 cases per 100 000 persons with HIV), while the NC had the lowest case counts and a stable incidence over time (from 54 to 64 cases per 100 000 persons with HIV).

Table 1. Number of cases and incidence of cryptococcal disease by South African province, GERMS-SA, 2022–2024.

Province	2022		2023		2024	
	n	Incidence risk (95% CI)†	n	Incidence risk (95% CI)†	n	Incidence risk (95% CI)†
Eastern Cape	682	77 (72–84)	683	76 (71–82)	623	69 (64–74)
Northern Cape	51	54 (40–71)	54	56 (42–74)	62	64 (49–82)
Western Cape	517	106 (97–115)	534	107 (98–116)	450	88 (80–96)

†Incidence risk was calculated using mid-year population denominators determined by the Thembisa model and is expressed as cases per 100 000 HIV-infected persons.

Figures 3A–C show the age-specific incidence of cryptococcal disease by sex and province. Incidence rates were calculated based on population denominators provided by Statistics South Africa and are expressed as cases per 100 000 population. Across all three provinces, incidence risk increased with increasing age, particularly in adults aged 30–49 years, and was consistently higher among males than females.

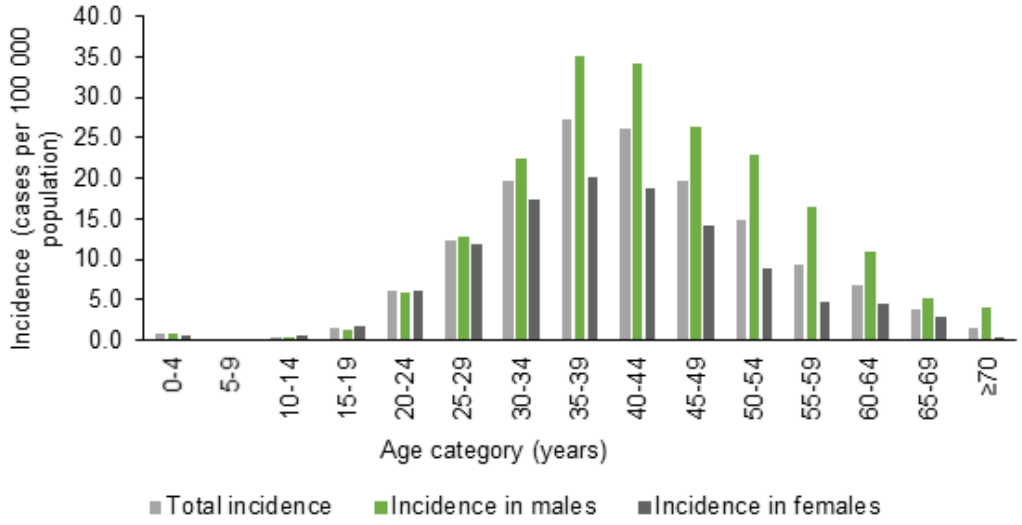


Figure 3A. Age-specific incidence for laboratory-confirmed cryptococcosis disease, reported to GERMS-SA, by sex, Eastern Cape province, South Africa, 2022-2024, N=1 842.

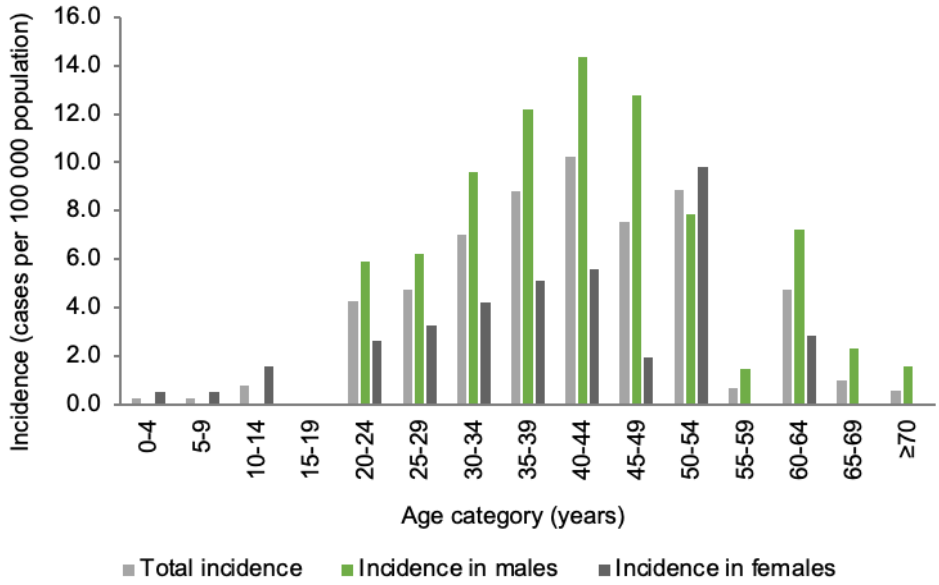


Figure 3B. Age-specific incidence for laboratory-confirmed cryptococcosis disease, reported to GERMS-SA, by sex, Northern Cape province, South Africa, 2022-2024, N=154.

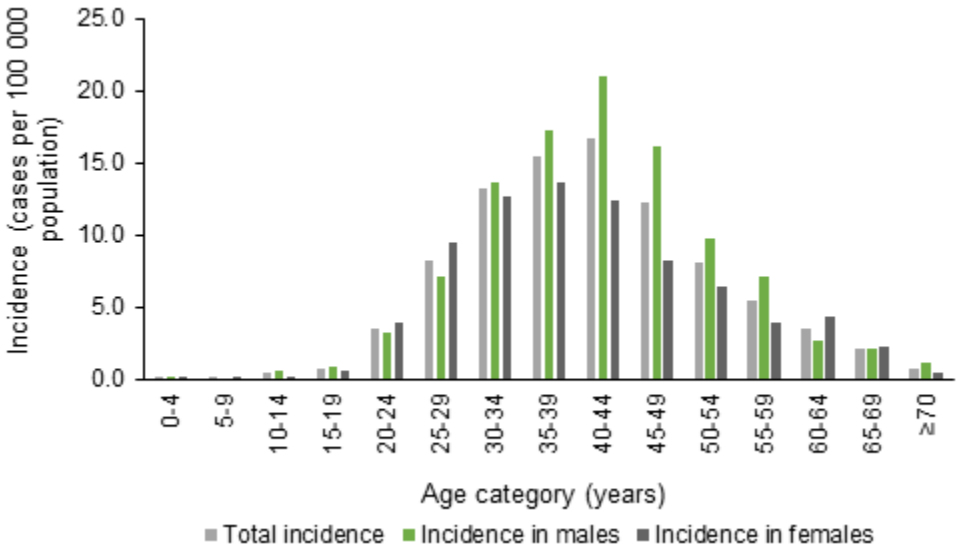


Figure 3C. Age-specific incidence for laboratory-confirmed cryptococcosis disease, reported to GERMS-SA, by sex, Western Cape province, South Africa, 2022-2024, N=1 473.

Clinical and HIV-related findings

During the study period, 83% (554/664) of cases at the ESS had clinical data available. Most cases were adults with a median age of 38 years (IQR: 32–45), with males representing the majority of infections (58%, 319/554, p=0.11) in the EC (60%, 216/359) and NC provinces (63%, 19/30), with a more balanced sex distribution observed in the WC (51%, 84/165 males) (Table 2).

Table 2 summarises the clinical characteristics of patients admitted to ESS. CSF was the predominant specimen type across all provinces at 94% (522/554), consistent with CM as the primary presentation. The majority of patients were living with HIV, with HIV seropositivity exceeding 90% in all provinces. Median CD4 counts were low (32, IQR: 13–63 cells/µL) across the provinces; 62% (342/554) of patients had a CD4 count of <50 cells/µL, and 6% (34/554) did not have documented CD4 counts. At hospital admission, current ART use among people with HIV was low – 16% (84/537) across provinces – while a high proportion (50% (271/537)) had interrupted or never-initiated treatment (31% (167/537)). Among those on ART with viral load results (87%, 73/84), the proportion with viral load suppression was 45% (33/73). Table 3 details HIV-related indicators and ART uptake by province.

Table 2. Overview of patient characteristics among cryptococcosis cases admitted to enhanced surveillance sites, GERMS-SA, Eastern, Northern and Western Cape provinces, South Africa, 2022–2024.

Characteristic	Eastern Cape N=359	Northern Cape N=30	Western Cape N=165
	n (% or IQR*)	n (% or IQR*)	n (% or IQR*)
Median age (years)	39 (33–46)	39 (28–41)	37 (29–45)
Age group (years)			
<15	1 (1)	1 (4)	3 (2)
15–29	56 (16)	9 (32)	35 (21)
30–44	195 (55)	13 (46)	83 (51)
45–59	91 (25)	4 (14)	36 (22)
60+	14 (3)	1 (4)	7 (4)
Unknown	2	2	2
Sex			
Female	143 (40)	11 (37)	81 (49)
Male	216 (60)	19 (63)	84 (51)
Specimen type			
CSF	336 (94)	29 (97)	157 (95)
Blood culture	21 (6)	1 (3)	6 (4)
Other*	2 (1)	0 (0)	2 (1)
HIV sero status			
Negative	4 (1)	0 (0)	13 (8)
Positive	355 (99)	30 (100)	152 (92)
ART treatment experience among people living with HIV			
Currently on ART	53 (20)	8 (44)	23 (29)
Previous ART	206 (80)	10 (56)	55 (71)
Unknown	96	12	74
CD4 count (cells/µl) among people living with HIV			
Median	33 (14–63)	42 (31–74)	29 (11–61)
<50	227 (66)	16 (59)	99 (66)
50–199	100 (29)	9 (33)	39 (26)
200–350	14 (4)	2 (7.4)	9 (6)
>350	3 (1)	0 (0)	2 (1)
Unknown	11	3	3
HIV-1 viral load (copies/mL)			
<400	59 (19)	2 (11)	28 (31)
400–10 000	32 (10)	2 (11)	7 (8)
>10 000	217 (70)	15 (79)	55 (61)
Antifungal induction regimen			
5FC-containing‡	272 (78)	19 (68)	98 (62)
Non-5FC§	48 (14)	6 (21)	36 (23)
No treatment	27 (8)	3 (11)	23 (15)
Unknown	12	2	8
Outcome at end of hospital admission			
Alive	229 (66)	21 (70)	101 (64)
Died	119 (34)	9 (30)	56 (36)
Unknown	11	0	8

IQR = interquartile range, 5FC = Flucytosine, CSF = cerebrospinal fluid. *Specimen type includes tissue and fluids. ‡5FC-containing = flucytosine in combination with fluconazole and/or amphotericin B. §Non-5FC = regimens without flucytosine which excludes monotherapy.

Table 3. HIV-related characteristics among patients with cryptococcosis admitted to enhanced surveillance sites, GERMS-SA, Eastern, Northern, and Western Cape provinces, South Africa, 2022–2024.

	Eastern Cape		Northern Cape		Western Cape	
Characteristics	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
Living with HIV	355		30		152	
New HIV diagnosis	355	52 (15)	30	6 (20)	152	28 (18)
Living with HIV currently on ART	355	53 (15)	30	8 (27)	152	23 (15)
Living with HIV interrupted ART	355	206 (58)	30	10 (33)	152	55 (36)
Living with HIV never on ART	355	95 (27)	30	11 (37)	152	61 (40)
Living with HIV currently on ART and viral load done	53	50 (94)	8	5 (63)	23	18 (78)
Living with HIV currently on ART and virally suppressed*	50	20 (40)	5	2 (40)	18	11 (61)

ART = antiretroviral therapy

*HIV viral load ≤400 copies/ mL

Antifungal treatment and outcomes

Flucytosine-containing regimens, in combination with fluconazole and/or amphotericin B, were the most prescribed (Table 2), particularly in the EC, where they accounted for the majority of all treatments (78%, 272/347). Among 483 patients with available treatment and outcome data, mortality among patients on flucytosine-containing regimens was 25% [(95/374), 95% CI: 21%–30%] across the three provinces, compared to 51% [(44/87), 95% CI: 40%–61%, p<0.001] among those treated without flucytosine (Table 4).

Table 4. Antifungal treatment regimens and in-hospital outcomes among patients with cryptococcosis, Eastern Cape (EC), Northern Cape (NC), and Western Cape (WC) provinces, South Africa, GERMS-SA, 2022–2024.

	5FC-containing regimen‡					Non-5FC regimen§					
Province	Alive¶ (n)	Died (n)	Total treated	Alive ¶ %	CFR % (95% CI)	Alive ¶ (n)	Died (n)	Total treated	Alive¶ %	CFR % (95% CI)	p-value
EC	195	66	261	75	25 (20–31)	19	29	48	40	60 (46–73)	p<0.001
NC	15	4	19	79	21 (8–45)	4	2	6	67	33 (8–73)	p=0.606
WC	69	25	94	73	27 (19–36)	20	13	33	61	39 (24–57)	p=0.189
Grand total	279	95	374	75	25 (21–30)	43	44	87	49	51 (40–61)	p<0.001

‡5FC-containing regimen=flucytosine in combination with fluconazole and/or amphotericin B

§Non-5FC = regimens without flucytosine which excludes monotherapy.

¶Discharged alive

Discussion

Cryptococcal disease remained a significant cause of illness and death among people living with HIV in the Eastern, Northern and Western Cape provinces. The demographic profile of cases, predominantly males aged 30–49 years, aligns with previous South African studies linking AHD and delayed healthcare engagement to poor outcomes. The higher number of cases among males may reflect differences in health-seeking behaviour, with men often accessing HIV testing and care later than women, resulting in more advanced immunosuppression at presentation. Lower retention in HIV care and delayed ART initiation among men in South Africa have been reported and may further increase their risk of opportunistic infections such as cryptococcosis.[3,14,15]

The high proportion of cases with CM and low median CD4 counts (<50 cells/µL) reflects persistent late HIV diagnosis and treatment interruptions.[2] These findings echo surveillance data from other African settings where cryptococcosis continues to mark advanced immunosuppression despite ART programme expansion.[8]

Notably, patients receiving flucytosine-containing regimens had substantially lower in-hospital mortality than those treated without flucytosine, although in the NC and the WC provinces, comparisons did not reach statistical significance because of small sample sizes. This supports robust international evidence demonstrating superior fungal clearance and reduced mortality with combination therapy including flucytosine.[9,10,11] These differences may also be partly explained by when and where patients received treatment. Flucytosine became more widely available in South Africa following its introduction through a national tender, meaning that patients treated earlier in the study period were more likely to have received non-5FC regimens. In addition, access to flucytosine may

have been limited to certain facilities, which could have influenced patient outcomes. Despite its broader availability, variability in pharmacy procurement and clinician familiarity with its use persist across facilities.[5,6,16,17] Ensuring consistent supply at a provincial depot and facility level and regular prescribing by clinicians remains a key implementation challenge.

Data incompleteness also influenced the interpretation of outcomes. Missing HIV status, incomplete CRFs, and undocumented treatment regimens accounted for most exclusions. These gaps likely underestimate disease severity and impede evaluation of provincial performance, particularly in the NC, where only 63% (30/48) of ESS cases had complete data. Missing outcome information in some treated patients further reduces precision in CFR estimates.

The overall provincial incidence pattern was consistent with previous reports.[5,6] The EC recorded the highest monthly case numbers and a stable incidence rate over the three years. The WC also reported high monthly counts but showed a clear decline in both case numbers and incidence risk in 2024, with a more balanced sex distribution than the other provinces. The NC reported the lowest and most stable case numbers, reflecting its smaller population and lower incidence risk. These provincial differences likely reflect variation in HIV prevalence, access to lumbar puncture and CrAg testing, health-seeking behaviour, and reporting completeness. The dip in 2024 may partly reflect disruptions during the NHLS laboratory information system breach in June and July. Strengthening ESS coverage and improving linkage of laboratory and clinical data will be important for more reliable trend analysis.

Study limitations

This study relied on routine public sector surveillance data and therefore does not include all laboratory-confirmed cryptococcal disease cases, particularly those diagnosed outside the public sector. The WC recorded a higher number of cases, partly because the province has more centralised laboratories and the ESS are located within these major referral hospitals. In the EC, enhanced surveillance is limited to facilities in Gqeberha, which means that cases from East London, Mthatha, and other smaller hospitals do not have clinical data collected. In the NC, data are primarily collected from the province's largest hospital, but the overall population size is much smaller, contributing to lower case numbers, and the absence of a dedicated surveillance officer for long periods further contributed to incomplete data. Post-discharge linkage to ART and mortality was not captured, and outcome data were therefore limited to in-hospital follow-up. Additionally, ART and viral load data were incomplete for some patients, potentially underestimating the extent of treatment interruption.

Conclusion

Between 01 January 2022 and 31 December 2024, cryptococcal disease continued to impose a substantial burden

across the EC, NC, and WC provinces, predominantly among adults with AHD. Mortality remained high but was lower among patients treated with flucytosine-containing regimens, supporting ongoing efforts to ensure consistent access to optimal antifungal therapy, including flucytosine.

Recommendations

1. The National and Provincial Departments of Health, together with hospital pharmacy managers, should ensure universal availability and appropriate use of flucytosine through strengthened procurement and facility-level stock monitoring by 2026.
2. Pharmaceutical manufacturers, supported by SAHPRA and the National Department of Health, should register flucytosine products in South Africa to prevent stockouts related to manufacturing.
3. Facility clinicians and HIV programme managers should ensure that patients who screen positive through routine CrAg screening are promptly and appropriately managed within the existing HIV programme.
4. NICD (GERMS-SA), Provincial Departments of Health, and participating facilities should enhance the completeness of surveillance data by expanding ESS coverage to under-represented facilities and improving linkage between laboratory and clinical datasets.
5. National and provincial HIV programmes, together with the NICD and academic partners, should support ongoing clinician training on the management of AHD and evidence-based antifungal therapy.
6. National and provincial HIV programmes and implementing partners should focus HIV testing and treatment integration activities on high-risk age groups and males to promote earlier diagnosis and sustained engagement in HIV care.

Acknowledgements

The GERMS-SA programme extends its gratitude to all laboratory and clinical staff at participating hospitals and NHLS laboratories across South Africa for their continued commitment to submitting isolates and completing case report forms. We thank the surveillance officers at ESS for their dedicated data collection efforts, as well as the patients who participated in this work despite challenging circumstances. Sincere appreciation is also extended to administrative staff at healthcare facilities, provincial co-ordinators, and NICD personnel whose contributions have made this surveillance possible. We acknowledge the ongoing support of the NICD and NHLS management, the National Department of Health, and our national and international collaborators. A full list of GERMS-SA contributors and partners is available in the main GERMS-SA 2023 report. See the GERMS-SA 2023 report at https://www.nicd.ac.za/wp-content/uploads/2024/12/GERMS-Annual-Review-2023.pdf

Ethics

Ethics approval for the surveillance programme was obtained from the Human Research Ethics Committee (Medical), University of Witwatersrand (clearance number M230985), and from relevant university and provincial ethics committees for ESS. Signed informed consent was obtained for patients who were interviewed at sentinel sites.[6]

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The NICD/NHLS funds these surveillance activities.

Conflicts of interest

The authors declare no conflicts of interest.

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