A comparison of cases of paediatric-onset and adult-onset cryptococcosis detected through population-based surveillance, 2005–2007

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Objective: We compared the epidemiology of laboratory-confirmed paediatric cryptococcal disease with adult-onset disease in the South African population.

Methods: The study was an active, prospective, population-based, laboratory-based surveillance in South Africa. We compared cases of paediatric cryptococcosis (<15 years) with cases of adult-onset cryptococcosis that were reported to the surveillance programme between 1 January 2005 and 31 December 2007. The case definition was based on a positive India ink test, cryptococcal antigen test or cryptococcal culture. Clinical case data were obtained at enhanced surveillance sites.

Results: Of 16 192 incident episodes of cryptococcosis in South Africa, 361 (2%) episodes occurred among children. In 2007, incidence was one and 19 cases per 100 000 persons in the general paediatric and adult populations and was 47 and 120 cases per 100 000 persons for HIV-infected children and adults, respectively. Among children, a bimodal peak in incidence was evident in the less than 1-year age group and in the 5 age group. Most children (64%) and adults (63%) were severely immunocompromised ($CD4^+$ T-lymphocyte cell count < 50 cells/μl) at the time of diagnosis. On multivariable analysis, children were significantly more likely than adults to be male, diagnosed on blood culture, infected with *Cryptococcus gattii,* treated with amphotericin B and admitted for a longer stay in hospital.

Conclusion: This series of 361 cases of paediatric cryptococcosis is by far the largest described to date. The diagnosis of cryptococcosis should be considered in the paediatric HIV-infected population, especially among those who are severely immunocompromised.

AIDS 2012, **26**:2307–2314

Keywords: cryptococcal meningitis, *Cryptococcus neoformans*, HIV, opportunistic infections, paediatric, South Africa, sub-Saharan Africa

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This work has been previously presented, in part, at the XVII International AIDS Conference; 3–8 August 2008; Mexico City, Mexico and, in part, at the Federation of Infectious Diseases Societies of South Africa 2nd Joint Congress; 28–31 October 2007; Cape Town, South Africa.

Received: 18 January 2012; revised: 25 May 2012; accepted: 15 June 2012.

DOI:10.1097/QAD.0b013e3283570567

Introduction

The fungus *Cryptococcus* has been well described as a cause of life-threatening disease among HIV-infected adults; however, little is known about the burden and epidemiology of cryptococcosis affecting children.

Cryptococcus spp. is ubiquitous in the environment, and it is thought that infection is acquired early on in life through the inhalation of infectious particles from the environment. Disease occurs later in life, usually associated with a severely compromised cell-mediated immune response [1].

In the late 1990s, incidence of cryptococcosis in the United States ranged from 1.8 to 6.7 cases per 100 000 persons in the general population [2]. Reports indicated that cryptococcosis affected 6–10% of the adult AIDS population in the era before HAART was available, with highest risk among those with a $CD4^+$ T-lymphocyte cell count of less than 100 cells/μl [3,4]. However, a study in South Africa in 2004 estimated an incidence of 15.6 cases per 100 000 persons in the general population; the incidence was 14 cases per 1000 persons living with AIDS [5].

Although cryptococcosis has been described to affect children, it is uncommon with fewer than 300 cases reported in the English language literature [5–15]. Little is known about why immunocompromised children develop the disease less frequently than immunocompromised adults. The three largest published series of paediatric cryptococcosis included 63 patients diagnosed over a 6-year period in the United States [6], 21 patients diagnosed over a 5-year period in Zimbabwe [7] and 30 patients diagnosed over a 10-year period in the United States [8]. In Gauteng province, South Africa, a surveillance study reported that 1% (24 of 2753) of new cases of cryptococcosis over a 2-year period occurred among children [5]. Studies have shown that most children only become infected with *Cryptococcus neoformans* after 2 years of age and that the disease affects older children (median age of 9.8 years) [1,8,15]. There have also been some case reports of cryptococcosis among neonates, suggesting vertical transmission of the infection [16,17].

This study compares the incidence and the epidemiology of laboratory-confirmed cryptococcal disease between South African children and adults diagnosed with laboratory-confirmed cryptococcal disease from 2005 to 2007.

Methods

Laboratory surveillance

Laboratory-confirmed cases of cryptococcosis were reported to the National Institute for Communicable Diseases (NICD) by 181 clinical microbiology laboratories, in the public, private, military and mining sectors, within South Africa, between 1 January 2005 and 31 December 2007.

A case of cryptococcosis in an individual was defined as a positive India ink test on cerebrospinal fluid (CSF) or a positive cryptococcal antigen test (on CSF, serum or urine) or culture of *Cryptococcus* species from any specimen site, performed at a participating microbiology laboratory. A child was defined as an individual less than 15 years of age at the time of specimen collection.

Cryptococcal isolates from individuals were sent to the Mycology Reference Laboratory at the NICD for confirmation of species-level identification and further characterization of the fungus, including differentiating *C. neoformans* and *Cryptococcus gattii* isolates using canavanine-glycine-bromothymol blue (CGB) agar [18,19]. These data were captured onto an *Epi Info* version 6.04d [Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, USA] database along with date of specimen collection, site from which specimen was collected and demographic details of the individual patient (including age and sex).

Clinical surveillance

Clinical data were obtained from persons diagnosed at 21 enhanced surveillance sites (ESSs) across South Africa. At the ESSs, trained surveillance officers completed a standardized case report form by reviewing hospital records and/or interviewing the patients. Clinical case data included discharge diagnosis, HIV status, $CD4^+$ T-lymphocyte cell count (absolute values only), antiretroviral use, duration of hospitalization, inhospital and outpatient antifungal treatment and outcome at the end of hospitalization. HIV testing at all ESSs was performed according to South African national policy: patients were screened with an HIV-1 ELISA. Among children aged less than 18 months, if the HIV-1 ELISA was positive, this was followed by confirmatory testing with a qualitative HIV-1 DNA PCR assay. For children at least 18 months old and adults, a positive HIV-1 ELISA was confirmed by a repeat ELISA using a second specimen. These data were also captured onto the *Epi Info* database.

Population denominators

Incidence for the South African population was calculated using denominators, obtained from Statistics South Africa [20]. Estimates of the number of HIV-infected persons in the South African population were obtained from the Actuarial Society of South Africa (ASSA) 2003 model [21]. These were used as denominators for calculating incidence of cryptococcosis in the HIV-infected population. For calculation of incidence, it was assumed that HIV prevalence among cryptococcal patients with known HIV status was similar to the prevalence for patients with unknown HIV status.

Ethical issues

Approval for the operation of the surveillance programme, review of medical records and patient interviews was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical), as well as from ethics committees at participating ESSs. Interviews were only conducted with patients (or their parents/legal guardians) who agreed to be interviewed by the surveillance officers and who provided full informed consent. In addition, assent was obtained from those children who were able to understand the informed consent process. Participants who did not consent to participate in the enhanced surveillance were still included as part of the laboratory surveillance, as demographic data and isolates were submitted to NICD.

Statistical analysis

Data analysis was performed after exclusion of all recurrent episodes of cryptococcosis by matching patient names, identity numbers, date of birth and/or hospital numbers to ensure that only incident episodes of cryptococcosis affecting individuals were counted. Univariate analysis of characteristics associated with disease among children and adults was performed using Fisher's exact test or the Mantel–Haenszel χ^2-test for categorical variables. For each univariate analysis, all available case information was used. Multivariable logistic regression models were evaluated, starting with all variables that were significant at P value less than 0.1 on univariate analysis, and dropping nonsignificant factors with stepwise backward selection. P values less than 0.05 were considered significant. All two-way interactions were evaluated. Univariate and multivariable analyses were performed with *Epi Info*, version 6.04d, and Stata version 9 (StataCorp Inc., College Station, Texas, USA).

Results

Laboratory surveillance

Between 1 January 2005 and 31 December 2007, 17 741 incident cases of cryptococcosis were reported. Of those, age was available for 16 192 (91%) patients, and children (<15 years of age) accounted for 2% (361 of 16 192) of all detected cases. Where data on sex were available for patients, the proportion of males was higher among children (194 of 355, 55%) than among adults (6 934 of 15 632, 44%) ($P < 0.001$).

Between 2005 and 2007, incidence of cryptococcosis increased from 0.54 to one case per 100 000 persons and from 13 to 19 cases per 100 000 persons for children and adults. Among paediatric patients, median age at time of diagnosis was 7 years (range 0–14 years); however, a bimodal peak in incidence of cryptococcosis was evident for children less than 1 year of age and for those in the 5 to 10-year age group across all years of surveillance (Fig. 1).

Details of the laboratory characteristics of cases of paediatric and adult-onset cryptococcosis are compared in Table 1. Of note, although *C. neoformans* caused most episodes of disease among both children and adults, children were significantly more likely than adults to be infected with *C. gattii* (9 vs. 3%, $P < 0.001$). Children were also significantly more likely than adults to be diagnosed by blood culture alone (11 vs. 4%, $P < 0.001$), even though most reported cases in both groups were diagnosed with laboratory-confirmed meningitis (88 vs. 97%, $P < 0.001$).

Clinical surveillance

Additional clinical data collected on patients from ESSs were available for 84 of 361 (23%) paediatric and 4 378 of 15 831 (28%) adult patients (Table 2). Where HIV status

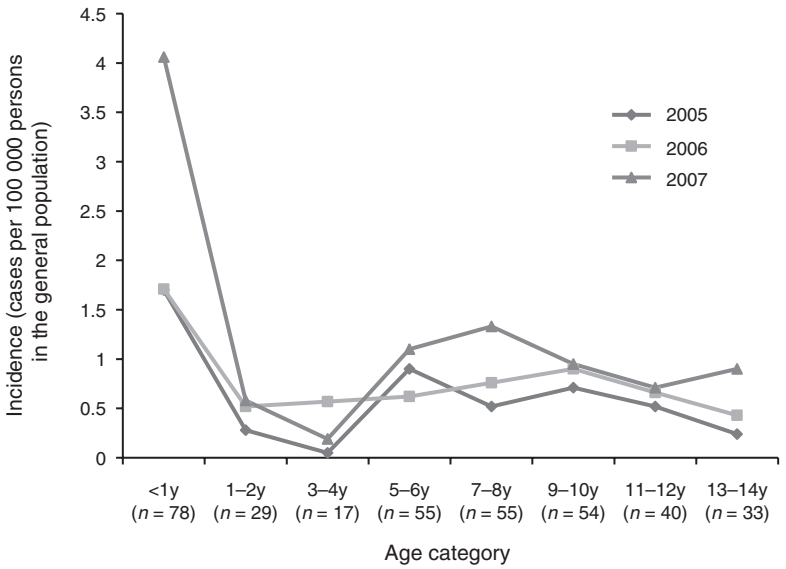

Fig. 1. Age-specific incidence for laboratory-confirmed cryptococcosis among children, South Africa, 2005–2007. $n = 361$.

Table 1. Comparison of laboratory characteristics of paediatric ($n = 361$) and adult ($n = 15\,831$) patients with cryptococcosis, South Africa, 2005–2007.

	Children (<15 years)	Adults (≥15years)	*P*
Species[a], *n* (%)			
Cryptococcus neoformans	168/184 (91)	11 694/12 002 (97)	<0.001
Cryptococcus gattii	13/184 (7)	301/12 002 (3)	
Other cryptococcal species[b]	3/184 (2)	7/12 002 (0.06)	
Specimen, *n* (%)			
Cerebrospinal fluid	319/361 (88)	15 179/15 831 (96)	<0.001
Blood	39/361 (11)	619/15 831 (4)	
Other (sputum, pleural fluid)	3/361 (1)	33/15 831 (0)	

[a]Viable fungal isolates were only available for speciation for 184 of 361 cases of paediatric cryptococcosis and 12 002 of 15 831 cases of adult cryptococcosis.
[b]Other cryptococcal species included *Cryptococcus albidus, Cryptococcus humicolis and Cryptococcus laurentii.*

was known, over 90% of patients were HIV-infected, although a smaller proportion of children was HIV-infected compared with adults (91% vs. 99%, $P < 0.001$). HIV test results were available for 74 children (88%): less than 1 year, nine of 12 (75%); 1–4 years, five of five (100%); 5–9 years, 35 of 37 (95%); and 10–14 years, 25 of 30 (83%). Eight of nine children (89%) aged less than 1 year old were HIV-infected. Most children (16 of 25, 64%) and adults (1 221 of 1943, 63%) who were HIV-infected and had a $CD4^+$ T-lymphocyte cell count performed had absolute $CD4^+$ T-lymphocyte cell values less than 50 cells/μl. Thirteen of 15 children with a recorded $CD4^+$ T-lymphocyte cell percentage were severely immunosuppressed (<15%). Significantly more children received amphotericin B as initiation therapy (54 vs. 43%, $P < 0.001$) and were treated for a longer period on amphotericin B (11 vs. 7 days, $P=0.005$) than adults. However, a smaller proportion of children was known to be discharged from hospital on fluconazole maintenance therapy (83 vs. 93%, $P = 0.007$).

On multivariable analysis, the following characteristics remained significant when comparing children and adults diagnosed with cryptococcosis at ESSs: children were more likely than adults to be male, diagnosed on blood culture, infected with *C. gattii,* treated with amphotericin B and admitted for a longer stay in hospital (Table 2).

In 2007, incidence of cryptococcosis in the paediatric HIV-infected population (47 cases per 100 000 persons) was lower than that in the adult HIV-infected population (120 cases per 100 000 persons); however, a peak in incidence was noted in the 10 to 14-year age category (517 cases per 100 000 persons).

When comparing seven paediatric and 30 adult HIV-uninfected patients with cryptococcal disease, most children and adults (six of seven, 86% vs. 16 of 26, 62%; $P = 0.23$) had other comorbid or immunocompromising conditions (aside from HIV infection). The three most common conditions in both groups included tuberculosis, head injury/hydrocephalus with a ventriculoperitoneal shunt *in situ* and a haematological malignancy. Although numbers were low, more children than adults were infected with *C. gattii* (two of two vs. none of 22, $P < 0.001$); *C. neoformans* was the most common causative agent overall for adult disease (21 of 22, 95%).

Discussion

This series of 361 paediatric cases of cryptococcosis detected over a 3-year period in South Africa is, by far, the largest described in the literature to date. We have shown that, although cryptococcal disease occurred less frequently among children than adults, it should not be thought of as an uncommon disease among children. In South Africa in 2007, the cryptococcal incidence among children less than 1 year was comparable to the incidence of *Haemophilus influenzae* meningitis among children less than 1-year (both stand at four cases per 100 000 population) [22].

Most paediatric and adult patients with cryptococcosis were HIV-infected and diagnosed with laboratory-confirmed *C. neoformans* meningitis; however, there was a higher proportion of HIV-uninfected children with cryptococcosis compared with adults with cryptococcosis. Similarly, compared with adults with cryptococcosis, children were more likely to be male, diagnosed on blood culture, *C. gattii*-infected, treated with amphotericin B and concurrently receiving HAART. However, children were less likely than adults to receive fluconazole maintenance therapy if they survived to be discharged from hospital.

In previous reports in the literature, the median age of children with cryptococcosis was 9.8 years of age and few cases of cryptococcosis had been reported among children less than 1 year of age [6–8,16,17]. In contrast, we have documented that the highest incidence occurs among children less than 1 year of age, with a second more sustained peak in incidence among children in

Table 2. Univariate and multivariable analysis of characteristics of children ($n = 84$) and adults ($n = 4378$) with cryptococcosis at enhanced surveillance sites, South Africa, 2005–2007.

Characteristics	Children (<15 years) *n/N*, %	Adults (≥15 years) *n/N*, %	Univariate analysis		Multivariable analysis	
			Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Year of infection						
2005	29/84 (35)	1200/4378 (27)	Reference	0.06		
2006	34/84 (40)	1561/4378 (36)	0.90 (0.55–1.49)			
2007	21/84 (25)	1617/4378 (37)	0.54 (0.30–0.95)			
Sex						
Female	36/84 (43)	2370/4373 (54)	Reference	0.04	Reference	0.007
Male	48/84 (57)	2003/4373 (46)	1.58 (1.02–2.44)		2.11 (1.22–3.62)	
Specimen						
Cerebrospinal fluid	67/84 (80)	4071/4378 (93)	Reference	<0.001	Reference	0.007
Other[a]	17/84 (20)	307/4378 (7)	3.36 (1.95–5.80)		2.80 (1.32–5.92)	
Species						
Cryptococcus neoformans	54/62 (87)	3613/3725 (97)	Reference	<0.001	Reference	0.001
Other cryptococcal species[b]	8/62 (13)	112/3725 (3)	4.78 (2.22–10.28)		3.94 (1.72–9.05)	
Inhospital case fatality ratio	22/81 (27)	1440/4326 (33)	0.75 (0.46–1.22)	0.24		
HIV-infected	67/74 (91)	3451/3481 (99)	0.08 (0.04–0.20)	<0.001		
$CD4^+$ T-lymphocyte cell count (HIV-infected individuals)						
≥50 cells/μl	9/25 (36)	722/1943 (37)	Reference	0.90		
<50 cells/μl	16/25 (64)	1221/1943 (63)	1.05 (0.46–2.39)			
Concurrent HAART at diagnosis	18/56 (32)	436/3198 (14)	3.00 (1.70–5.31)	<0.001		
Treatment for cryptococcosis						
Fluconazole induction therapy	21/82 (26)	1948/4303 (45)	Reference	<0.001	Reference	0.02
Amphotericin B induction therapy	44/82 (54)	1861/4303 (43)	2.19 (1.30–3.70)		2.40 (1.23–4.66)	
No treatment prescribed in hospital	17/82 (21)	494/4303 (12)	3.19 (1.67–6.10)		2.09 (0.80–5.43)	
Survivors discharged on fluconazole	39/47 (83)	2399/2576 (93)	0.36 (0.17–0.78)	0.02		
Duration of hospitalization						
<7 days	17/81 (21)	1428/4314 (33)	Reference	<0.001	Reference	0.01
7–13 days	16/81 (20)	1362/4314 (32)	0.99 (0.50–1.96)		1.07 (0.46–2.48)	
14–20 days	21/81 (26)	883/4314 (20)	2.00 (1.04–3.81)		1.99 (0.87–4.52)	
≥21 days	27/81 (33)	641/4314 (15)	3.54 (1.91–6.54)		3.18 (1.42–7.12)	
Time from admission to specimen collection for diagnosis of cryptococcosis						
Diagnosed as an outpatient	2/84 (2)	153/4374 (4)	Reference	0.03		
0–6 days	73/84 (87)	4074/4374 (93)	1.37 (0.33–5.64)			
7–13 days	6/84 (7)	99/4374 (2)	4.64 (0.92–23.43)			
≥14 days	3/84 (4)	48/4374 (1)	4.78 (0.77–29.46)			
Time from admission to start of antifungal therapy						
<2 days	36/65 (55)	2522/3770 (67)	Reference	0.12		
2–6 days	21/65 (32)	992/3770 (26)	1.48 (0.86–2.55)			
7–13 days	4/65 (6)	178/3770 (5)	1.57 (0.55–4.47)			
≥14 days	4/65 (6)	78/3770 (2)	3.59 (1.25–10.34)			

CI, confidence interval; OR, odds ratio.
[a]Other included blood [16 of 17 (94%) children, 300 of 307 (98%) adults] and other specimens.
[b]Other cryptococcal species included *Cryptococcus gattii* [seven of eight (88%) children, 109 of 112 (97%) adults] and other less common cryptococcal species.

the 5–10-year age group. As most paediatric HIV infection in South Africa is vertically transmitted from mother to child, and as cryptococcosis is an AIDS-defining illness, the bimodal distribution in cryptococcal incidence rates among children may be explained by the occurrence of cryptococcal disease among rapid and slow HIV progressors [23,24].

Cryptococcal disease caused by *C. gattii* among South Africans has been described previously [25]. Although symptoms, diagnosis and treatment of this form of cryptococcosis are similar to *C. neoformans*, it has been shown to occur slightly more frequently among immunocompetent individuals [25]. In this study, significantly more children than adults were infected with *C. gattii*, although the numbers were very small.

In South Africa, children are more likely than adults to have a blood culture sent for laboratory investigation (C. Cohen, personal communication). This could explain why more children than adults were diagnosed with cryptococcosis on blood culture alone. Laboratory diagnosis of cryptococcaemia (and perhaps CSF cultures) among children may occur as a chance finding rather than confirmation of a clinical suspicion of the disease.

Our findings show that most cases of cryptococcal disease occurred among HIV-infected individuals with very low absolute $CD4^+$ T-lymphocyte cell counts, and only 26% of the HIV-infected children with cryptococcal disease were on HAART at the time of illness. These findings may be a reflection of the inadequate uptake of South Africa's Prevention of Mother to Child Transmission

(PMTCT) programme in the earlier years [26]. Implementation of this programme has dramatically improved since the completion of this study [27] and incidence of cryptococcosis may be lower in the South African paediatric population born after 2007.

The extremely high peak in the estimated incidence of cryptococcosis among HIV-infected children between 10 and 14 years of age was an unexpected finding in our study (517 cases per 100 000 persons), as the overall population incidence of cryptococcosis between 10 and 14 years ranged from 0.5 to 0.9 cases per 100 000 persons. The high peak in this HIV-infected group of individuals may be due to an underestimation of the number of HIV-infected persons in the 10 to 14-year age category by the ASSA-2003 model (1.7% HIV prevalence among 10 to 14-year olds, 2005). The ASSA model may need to be revised to depict the true prevalence of HIV infection in this subcategory of individuals [28].

Amphotericin B induction treatment was prescribed more commonly for children than adults. However, less than one-third of children and adults received amphotericin B which is the recommended antifungal drug for management of cryptococcal disease among HIV-infected persons in South Africa [24]. Also, the median time on amphotericin B therapy was less than the recommended time of 14 days for treatment of incident disease [median of 10 days for children and 7 days for adults ($P = 0.005$)] [29]. Fewer children than adults were discharged on fluconazole maintenance therapy to prevent recurrence of cryptococcal disease. This may be due to the attending paediatricians' unfamiliarity with the treatment guidelines for cryptococcosis, as it is mainly considered an adult-onset disease, or lack of availability of the paediatric fluconazole suspension.

This study has several limitations. First, as only laboratory-confirmed disease was reported to surveillance, we believe that the incidence of cryptococcosis reported here underestimates the true burden of disease for both paediatric and adult patients, as many individuals may have been too ill to access the healthcare services or may not have had specimens taken to diagnose their illness. This may also explain the lower incidence of cryptococcosis in the South African HIV-infected population when compared with the United States HIV-infected population in the pre-HAART era [2–5]. Second, clinical data were only available for patients diagnosed at ESSs (4 462 of 16 192, 28%). When demographic and laboratory data of cases from non-ESSs were compared to those of cases from ESSs, that is, age distribution, sex, specimen type and cryptococcal species, adults from ESSs were significantly more likely to be diagnosed with cryptococcal disease on blood culture alone than adults from non-ESSs (7 vs. 3%, $P < 0.001$) (data not shown). There was also a significant difference in the age distribution of cases between ESSs and non-ESSs ($P = 0.02$) (data not shown). These differences may have biased the study findings. Third, as this was an observational study, many of the clinical datasets were incomplete which may also have impacted on the study results. Fourth, the clinical data collected from these individuals were taken from routinely collected surveillance data and a number of shortcomings using this method have been identified. These include the lack of detailed clinical information regarding presenting symptoms in patients, detailed inhospital management of individuals and long-term complications of the disease. We also did not have sufficient information to classify episodes of cryptococcosis occurring as a result of immune reconstitution inflammatory syndrome. We also believe that the true case–fatality ratio (although relatively high) of cryptococcal disease is underestimated, as many individuals may have died following their discharge from hospital [30].

Although infection cannot be prevented because *Cryptococcus* spp. is ubiquitous in the environment, disease can be prevented. HIV-infected children should be started on HAART when indicated, prior to them becoming severely immunocompromised and at increased risk of developing cryptococcal disease. South Africa will implement screening for cryptococcal antigenaemia among patients with $CD4^+$ T-lymphocyte cell counts less than 100 cells/μl followed by preemptive treatment to prevent meningitis-related deaths in 2012 [31]. Although children are not being specifically targeted, the laboratory-based screening programme will include patients of all ages and may improve early diagnosis of paediatric cryptococcosis.

In this study, we have clearly shown that cryptococcosis does occur among children, especially those infected with HIV and with a low $CD4^+$ T-lymphocyte cell count. Therefore, the diagnosis of cryptococcosis must be considered in the paediatric HIV-infected population, especially among those found to be severely immunocompromised.

Acknowledgements

Study design was done by N.P.G., K.M.M., C.C. and S.T.M.

Data collection and management was performed by S.T.M., V.C.Q., N.P.G., H.D., A.C.W., A.S.K. and K.M.M.

Data analysis was performed by S.T.M., N.P.G. and C.C.

Writing and critical review of manuscript was done by N.P.G., S.T.M., C.C., V.C.Q., H.D., A.C.W., A.S.K. and K.M.M.

The authors would like to thank all clinical and laboratory staff throughout South Africa for submitting case reports and isolates for the Group for Enteric, Respiratory and Meningeal disease Surveillance in South Africa (GERMS-SA) national surveillance programme as well as all the patients who agreed to provide further clinical details.

GERMS-SA 2005–2007:

Sandeep Vasaikar (Eastern Cape); Nolan Janse van Rensberg, André Möller, Peter Smith, Anne-Marie Pretorius (Free State); Khatija Ahmed, Anwar Hoosen, Ruth Lekalakala, Pyu Pyu Sein, Charles Feldman, A.S.K., Olga Perovic, Jeannette Wadula, Mike Dove, Kathy Lindeque, Linda Meyer, Gerhard Weldhagen (Gauteng); Stan Harvey, Pieter Jooste (Northern Cape); Danie Cilliers (North West Province); Wim Sturm, Trusha Vanmali, Prathna Bhola, Prashini Moodley, Sindiswe Sithole, H.D. (KwaZulu Natal); Ken Hamese (Limpopo); Keith Bauer, Greta Hoyland, Jacob Lebudi, Charles Mutanda (Mpumalanga); Rena Hoffmann, Siseko Martin, Lynne Liebowitz, Elizabeth Wasserman, A.C.W. (Western Cape); Adrian Brink, Inge Zietsman, Maria Botha, Xoliswa Poswa, Mark da Silva, Suzy Budavari (Ampath laboratories); Claire Heney, Juanita Smit (Lancet laboratories); Marthinus Senekal (Pathcare Laboratories); C.C., Mireille Cheyip, Leigh Dini, Linda de Gouveia, John Frean, Susan Gould, Karen Keddy, K.M.M., S.T.M., Elizabeth Prentice, V.C.Q., Jeffrey Ramalivhana, Arvinda Sooka, Anne von Gottberg and N.P.G. (National Institute for Communicable Diseases/ NHLS).

Development of this publication was supported by the Health and Human Services (HHS) Centers for Disease Control and Prevention (CDC), National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP) and Global AIDS Program (GAP) Cooperative Agreement U62/PSO022901. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of CDC.

Conflicts of interest

N.P.G. has received an honorarium from MSD South Africa for a single speaking engagement and has received a research grant from Pfizer South Africa for an unrelated surveillance project. H.D. has received an honorarium from MSD South Africa for a single speaking engagement and a travel grant from Novartis South Africa. For the remaining authors, none are declared.

In 2005–2006, the study was funded by the United States Agency for International Development's Antimicrobial Resistance Initiative, transferred via a cooperative agreement (number U60/CCU022088) from the CDC, Atlanta, Georgia, USA.

In 2005–2007, the study was also supported by the CDC, NCHHSTP and GAP Cooperative Agreement U62/PSO022901.

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