Cryptococcosis in Gauteng: Implications for monitoring of HIV treatment programmes

Kerrigan M McCarthy, Cheryl Cohen, Helen Schneider, Susan M Gould, Mary E Brandt, Rana A Hajjeh, for the Gauteng Cryptococcal Surveillance Initiative Group

To the Editor: In South Africa, for reasons of confidentiality, difficulties with case definition and surveillance logistics, AIDS and AIDS-defining opportunistic infections are not notifiable. South African government authorities and non-governmental organisations have difficulty measuring the burden of disease due to HIV/AIDS, or obtaining objective evidence for effectiveness of interventions such as antiretroviral therapy (ART) to mitigate its impacts. Numbers of AIDS cases are inferred from mathematical models and population death rates. Data from a surveillance project for cryptococcosis (CC) in Gauteng,[1] and similar data from the pre-ART era in North America,[2] indicate that 1.4 - 6.6% of people with AIDS become ill with CC, an AIDS-defining illness and opportunistic infection that is preventable in the context of ART. In South Africa the introduction of ART may decrease deaths due to AIDS. We present incidence rates for CC, HIV seroprevalence data and number of deaths due to AIDS and propose that incidence rates of CC are good although crude markers of the effectiveness of HIV testing and treatment programmes.

Methods

Population-based surveillance for CC was conducted in Gauteng province, South Africa, from 1 March 2002 to 29 February 2004,[1] facilitating calculation of incidence rates and geographical distribution of cases. Demographic data for the population of Gauteng, including district and subdistrict population numbers, and numbers of health care facilities able to admit and treat CC in the province, were obtained from the October 2001 census (Statistics South Africa, Report No. 03-02-03 (2001) and the Health Information System, Gauteng Province). Estimated HIV denominators for the Gauteng population living with HIV/AIDS were obtained from the Actuarial Association of South Africa model.[3] Age-related HIV seroprevalence estimates were obtained from the Nelson Mandela HSRC study of HIV/AIDS.[4] Estimates of the number of deaths due to AIDS were obtained from the MRC report.[5] Results from the Annual HIV and Syphilis Seroprevalence Survey of Women Attending Public Antenatal Clinics in Gauteng (unpublished survey) were used with permission.

Results

From 1 March 2002 to 29 February 2004, 2 753 incident cases of CC were identified. The incidence rate was 15.6/100 000 per annum (males 15.2/100 000, females 15.8/100 000) (Fig. 1). Using mathematically modelled data to obtain population sizes of people living with HIV and sick with AIDS, the incidence rate was 95/100 000 HIV-infected persons, and 14/1 000 people living with AIDS. Given the number of assumptions being made, these rates represent estimates of disease burden. During this period 4 - 17% of patients with CC resident in each district were admitted to a Gauteng hospital situated outside their district of residence, with the exception of Metsweding District Municipality, which has no public hospital capable of managing inpatients with CC. Death rates attributable to HIV/AIDS in Gauteng for 2000 and the age-adjusted incidence of CC peak in the same age category (35 - 44 years) (Fig. 2). The West Rand District Municipality had the highest HIV seroprevalence rate among antenatal clinic attendees in 1999, 2000 and 2003 (27.2%, 35.8% and 38.8%, respectively), as well as the highest incidence of CC during 2002 - 2004 (40.9%). Among men and women living with HIV, the incidence rates of CC differ by gender in the same way that HIV seroprevalence does, with the highest gender-related incidence in males (age category 35 - 39 years; incidence 39 cases/100 000 general population) occurring at an older age than females (peak at age category 30 - 34 years; incidence 36 cases/100 000 general population).

Discussion

We have demonstrated that the demographics of patients with CC match the demographics of South Africans living with HIV and dying from AIDS with respect to age, gender and

Reproductive Health and HIV Research Unit, Department of Obstetrics and Gynaecology, University of the Witwatersrand, Johannesburg
Kerrigan M McCarthy, MB BCh, DTM&H, FCPath (SA) Micro

Epidemiology and Surveillance Unit, National Institute for Communicable Diseases of the National Health Laboratory Service, and School of Public Health, University of the Witwatersrand
Cheryl Cohen, MB BCh, DTM&H, MSc (Epi), FCPath (SA) Micro

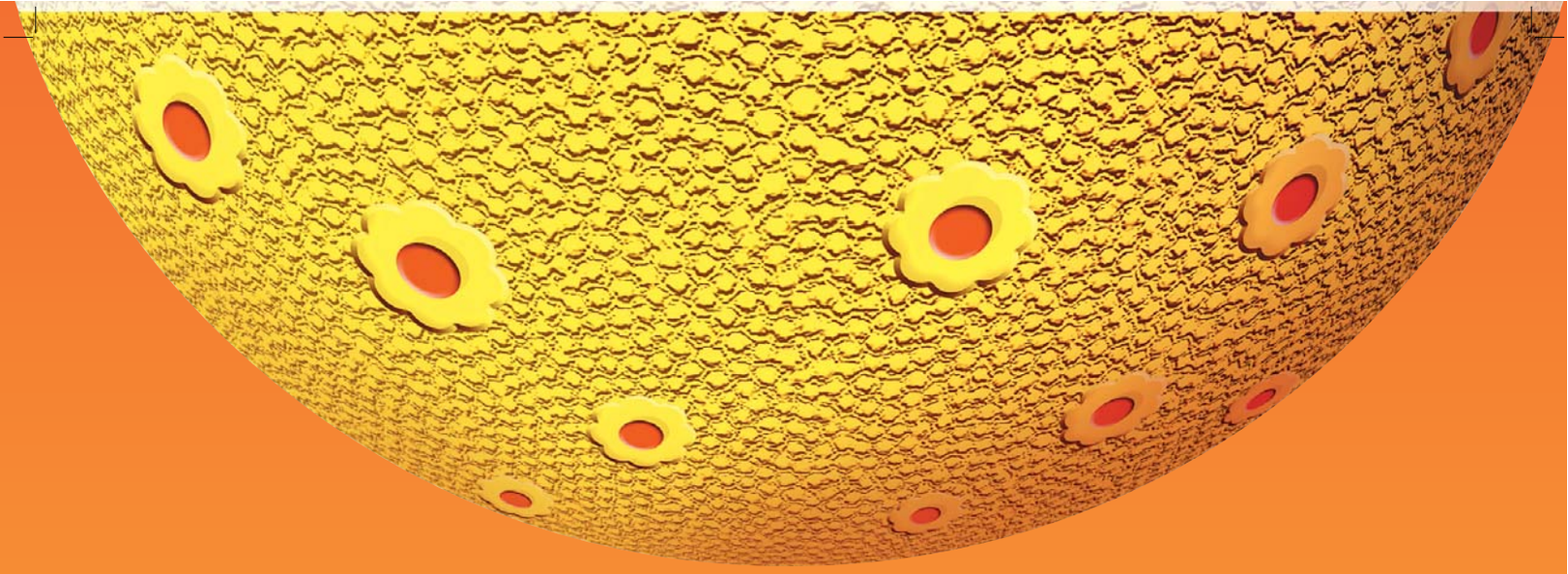
Centre for Health Policy, School of Public Health, University of the Witwatersrand
Helen Schneider, MB ChB, MMed (Public Health)

Mycology Reference Unit, National Institute for Communicable Diseases of the National Health Laboratory Service, and Division of Virology and Communicable Diseases Surveillance, University of the Witwatersrand
Susan M Gould, BSc Hons, DipMedTech

Mycotic Diseases Branch, Coordinating Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, USA
Mary E Brandt, PhD

Division of Bacterial Diseases, Coordinating Center for Infectious Diseases, Centers for Disease Control and Prevention
Rana A Hajjeh, MD

Corresponding author: *K McCarthy (kmccarthy@rhru.co.za)*



The clear choice ...

... when the diagnosis isn't

BROAD SPECTRUM WITHOUT COMPROMISING EFFICACY IN ASPERGILLOSIS AND CANDIDIASIS[1,2,3]

S4 AmBisome
liposomal amphotericin B
Reg. No. 36/20.2.2/0453

Breadth. Depth. Duration

AmBisome® for Injection S4 ABBREVIATED PRESCRIBING INFORMATION. Presentation: A sterile lyophilised product for intravenous infusion. Each vial contains 50 mg of amphotericin B.P., encapsulated in liposomes. Indications: The treatment of severe systemic and/or deep mycoses where toxicity (particularly nephrotoxicity) precludes the use of conventional systemic amphotericin B in effective dosages. The empirical treatment of presumed fungal infections in febrile neutropenic patients, where the fever has failed to respond to broad-spectrum antibiotics and appropriate investigations have failed to define a bacterial or viral cause. Dosage & Administration: Preparation – Follow the reconstitution instructions exactly as given in the SmPC. Administration – AmBisome® should be administered by intravenous infusion over a 30 – 60 minute period. The recommended concentration for infusion is 0.2 mg/ml to 2.0 mg/ml. Therapy for systemic and/or deep mycoses is usually instituted at a daily dose of 1.0 mg/kg of body weight, and increased stepwise to 3.0 mg/kg, as required. Data are presently insufficient to define total dosage requirements and duration of treatment necessary for resolution of mycoses. However, a cumulative dose of 1.0 – 3.0 g of amphotericin as AmBisome® over 3 – 4 weeks has been typical. Dosage of amphotericin as AmBisome® must be adjusted to the specific requirements of each patient. The recommended dose in febrile neutropenia is 3 m g/kg body weight per day. Treatment should be continued until the recorded temperature is normalised for 3 consecutive days. In any event, treatment should be discontinued after a maximum of 42 days. Children have been successfully treated with AmBisome® without reports of unusual adverse events and have received comparable doses to adults on a per kilogram body weight basis. There are no specific dosage recommendations or precautions for elderly patients. Contra-Indications: Hypersensitivity to any of the constituents of AmBisome®, unless the condition requiring treatment is life threatening and amenable only to AmBisome® therapy. Warnings: Although anaphylactic or severe allergic reactions are rare, administration of a test dose is still advisable. If a small amount of AmBisome® (e.g. 1 mg) can be administered for about 10 minutes without severe allergic reactions within 30 minutes the dose can be continued. Laboratory evaluation of renal, hepatic and haematopoietic function should be performed at least weekly and particular attention should be given to patients receiving concomitant therapy with nephrotoxic drugs. Levels of serum potassium and magnesium should be monitored regularly. Use in diabetic patients: Each vial of AmBisome® contains approximately 900 mg of sucrose. Use in dialysis patients: Haemodialysis or peritoneal dialysis does not appear to affect the elimination of AmBisome® and data suggest no dose adjustment is required, however administration should be avoided during the haemodialysis procedure. Use in pregnancy: As safety of AmBisome® in pregnancy has not been established, the risk/benefit ratio must be considered. Side effects: Generally patients who developed renal dysfunction while receiving conventional amphotericin, improved or stabilised when AmBisome® was substituted even when doses were increased. In trials, fewer patients suffered infusional or renal toxicity with AmBisome®, than with either conventional amphotericin B or amphotericin B lipid-complex. Infusion reactions include fever, chills/rigors, back pain, chest tightness, dyspnoea, bronchospasm, flushing, tachycardia and hypotension, and these resolve with cessation of the infusion. Additional adverse events observed in clinical trials include nausea, vomiting, hypokalaemia, creatinine and BUN increase, hypomagnesaemia, hypocalcaemia, hyperglycaemia, hyponatraemia, liver function test abnormalities, diarrhoea, abdominal pain, headache and rash. Convulsion, thrombocytopenia and anaphylactoid reactions have been reported rarely. Overdosage: In clinical trials, repeated daily doses up to 15 mg/kg in adults and 10 mg/kg in children have been given without reported dose-dependent toxicity. If overdosage occurs, stop administration immediately and carefully monitor hepatic, renal and hematopoietic function. Interactions: No clinically significant drug interactions have been observed in clinical trials to date. Pharmaceutical Precautions: Do not store above 25°C. Do NOT freeze. Protect from light. Reconstituted product may be stored for up to 24 hours at 2 – 8°C. Infusion of AmBisome® should commence within 6 hours of dilution with 5% dextrose. DO NOT STORE partially used vials. DO NOT RECONSTITUTE AmBisome® WITH SALINE, OR MIX WITH OTHER DRUGS OR ELECTROLYTES. Legal category: Package Quantities: Cardboard carton of 10 vials each. Product Registration Number: 36/20.2.2/0453. Full prescribing information is available from the marketing authorisation holder: Key Oncologics (Pty) Ltd Building 3, Glenhove Square 71- 4th Street Houghton Estate 2198 South Africa. CONSULT THE SUMMARY OF PRODUCT CHARACTERISTICS BEFORE PRESCRIBING. Date of preparation: May 2004. AmBisome® is a trademark.

K•E•Y ONCOLOGICS
Your Key Partner

PIASA Member Company

1. Ambisome, Summary of Product Characteristics. 2. Cornely O et al. The 47th American Society of Hematology Annual Meeting and Exposition 2005; Poster 3222. 3. Ringdén O et al. *J Antimicrob Chemother* 1991; 28 (Suppl B): 73-82.

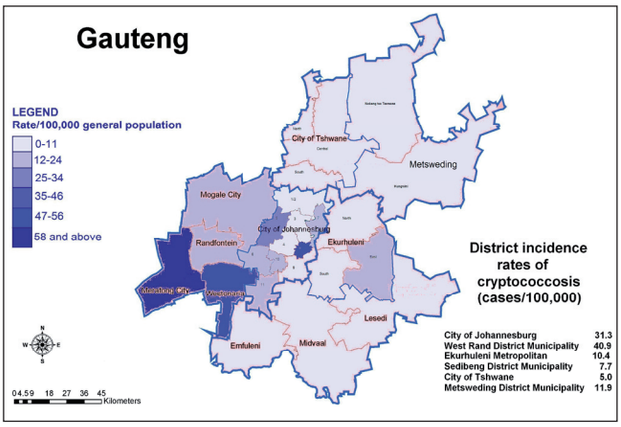


Fig. 1. Regions of Gauteng showing incidence of cryptococcosis by sub-district, 2002 - 2004.

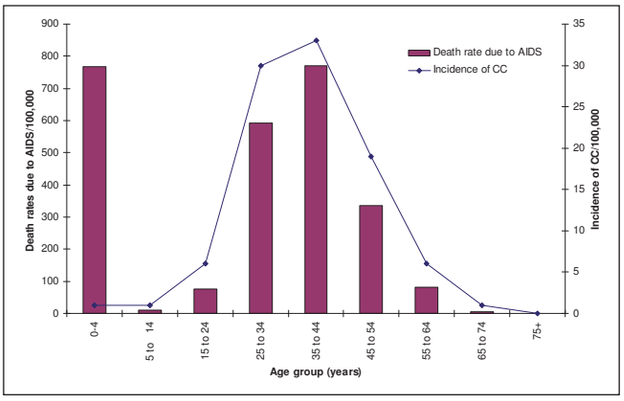


Fig. 2. Death rates attributable to HIV/AIDS in Gauteng, 2000,[5] and age-adjusted incidence of cryptococcosis (CC) in Gauteng, 2002 - 2004.

geographical location within Gauteng. We propose that CC has the characteristics of an ideal opportunistic infection for monitoring the effectiveness of HIV testing and treatment programmes in South Africa, for the following reasons.

Firstly, laboratory-based surveillance programmes are likely to identify a substantial proportion of patients with CC because the predominant manifestation of meningoencephalitis is severe headache, which makes health-seeking behaviour by patients inevitable; the diagnosis of CC cannot be made clinically and lumbar puncture with laboratory testing is required; incident cases of cryptococcal meningitis are not treated empirically, unlike bacterial meningitis; and the inexpensive India ink test is readily available in all laboratories in South Africa and has excellent sensitivity in national surveillance compared with culture to identify cases of cryptococcal meningitis.

Secondly, in the context of the HIV/AIDS epidemic, there is sufficient burden of disease due to CC to ensure that surveillance is worth while and meaningful. CC has been observed to be the third most common cause of death in South African ART treatment programmes (personal communication, Dr Andrew Boulle, University of Cape Town, 3rd PACT Conference, Johannesburg, 16 - 18 October 2007).

Finally, population-based studies have demonstrated a significant reduction in the incidence of CC in the post-ART era,[6] with one study demonstrating a 10-fold reduction in incidence among the general population from 4/100 000 to 0.4/100 000.[2]

In the context of providing comprehensive HIV/AIDS care and treatment, continued occurrence of CC points to patient failure or inability to access medical care for HIV, or inadequate monitoring of its progress and failure to initiate ART.[6] CC will continue to occur in the context of immune reconstitution disease. However, these individuals commonly have CD4 counts under 100 cells/μl at the time of ART initiation, and may therefore still represent failure of timeous initiation of ART. The incidence of CC in HIV-negative persons in the USA is less than 1/1 000 000 general population and has remained unaltered in the post-ART era.[2]

We anticipate substantial reductions in the incidence of CC in South Africa over the next decade. The Group for Enteric, Respiratory and Meningitis Surveillance of South Africa (GERMS-SA) of the National Institute for Communicable Diseases performs national laboratory-based surveillance for CC throughout South Africa (commenced January 2005), and is ideally placed to monitor changes in incidence of CC as the provision of HIV services expand.

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the CDC.

The study was funded by a CDC contract with the NHLS, South Africa.

References

1. McCarthy KM, Morgan J, Wannemuehler KA, *et al*. Population-based surveillance for cryptococcosis in an antiretroviral-naive South African province with a high HIV seroprevalence. *AIDS* 2006; 20(17): 2199-2206.
2. Mirza SA, Phelan M, Rimland D, *et al*. The changing epidemiology of cryptococcosis: an update from population-based active surveillance in 2 large metropolitan areas, 1992-2000. *Clin Infect Dis* 2003; 36(6): 789-794.
3. Dorrington R, Bradshaw D, Budlender D. *HIV/AIDS Profile of the Provinces of South Africa: Indicators for 2002*. Cape Town: Actuarial Society of Southern Africa, 2002. http://www.mrc.ac.za/bod/AIDSindicators2002.pdf (accessed 19 April 2008).
4. Shisana O, Simbayi L. *Nelson Mandela HSRC Study of HIV/AIDS: Full Report*. Cape Town: Human Sciences Research Council, 2007.
5. Bradshaw D, Groenewald P, Laubscher R, *et al*. Initial burden of disease estimates for South Africa, 2000. *S Afr Med J* 2003; 93(9): 682-688.
6. Dromer F, Mathoulin-Pelissier S, Fontanet A, Ronin O, Dupont B, Lortholary O. Epidemiology of HIV-associated cryptococcosis in France (1985-2001): comparison of the pre- and post-HAART eras. *AIDS* 2004; 18(3): 555-562.

Accepted 7 November 2007.