The estimated burden of fungal disease in South Africa

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Background. With a population of 56.5 million, over 7 million persons living with HIV, one of the world's highest rates of tuberculosis (TB) and a large proportion of the population living in poverty, South Africa (SA)'s fungal disease burden is probably substantial and broad in scope.
Objectives. To estimate the burden of fungal disease in SA.
Methods. Using total and at-risk populations and national, regional and occasionally global data, we estimated the incidence and prevalence of the majority of fungal diseases in SA.
Results. Estimates for the annual incidence of HIV-related life-threatening fungal disease include cryptococcal meningitis (8 357 cases), *Pneumocystis* pneumonia (4 452 cases) and endemic mycoses (emergomycosis, histoplasmosis and blastomycosis, with 100, 60 and 10 cases per year, respectively). We estimate 3 885 cases of invasive aspergillosis annually. The annual burden of candidaemia and *Candida* peritonitis is estimated at 5 421 and 1 901 cases, respectively. The epidemic of pulmonary TB has probably driven up the prevalence of chronic pulmonary aspergillosis to 99 351 (175.8/100 000), perhaps the highest in the world. Fungal asthma probably affects >100 000 adults. Mucosal candidiasis is common, with an annual prevalence estimated at 828 666 and 135 289 oral and oesophageal cases, respectively, complicating HIV infection alone (estimates in other conditions not made), and over a million women are estimated to be affected by recurrent vulvovaginal candidiasis each year. Tinea capitis in children is common and conservatively estimated at >1 000 000 cases. The inoculation mycoses sporotrichosis, chromoblastomycosis and eumycetoma occur occasionally (with 40, 40 and 10 cases estimated, respectively). Overall, we estimate that over 3.2 million South Africans are afflicted by a fungal disease each year (7.1% of the population).
Conclusions. Significant numbers of South Africans are estimated to be affected each year by fungal infections, driven primarily by the syndemics of HIV, TB and poverty. These estimates emphasise the need for better epidemiological data, and for improving the diagnosis and management of these diseases.

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Fungal infections are common and diverse in South Africa (SA), driven in large part by the syndemics of HIV, tuberculosis (TB) and poverty. SA has the dubious distinctions of having the largest HIV epidemic,[1] one of the highest incidences of TB,[2] and – by some measures – the most socioeconomic inequity[3] in the world. Each of these conditions on its own or in combination can predispose individuals to fungal disease, but to our knowledge, the burden of such infections in SA has not previously been estimated.

Objectives

To estimate the prevalence and incidence of fungal infections in SA, excluding cutaneous infections with the sole exception of tinea capitis because of its severity in a significant minority of children.

Methods

The burden of fungal disease in SA was estimated using the methodologies of LIFE-worldwide.org.[4] Starting estimates for fungal disease or for conditions complicated by fungal disease were obtained by review of the English language literature. National or local data were preferred, but where these were unavailable, data were extrapolated from other sources in order of decreasing preference: from other countries in southern Africa, elsewhere in Africa, non-African middle-income countries, and non-African non-middle-income countries. We also calculated 25% sensitivity bounds (25% lower and 25% higher than the base estimate) to reflect uncertainty in these estimates.

Prevalence data for conditions that may become complicated by fungal infections were obtained from national surveys, registries or published estimates (Table 1). SA population estimates and HIV-related deaths were obtained from Statistics South Africa.[5] The number of people living with HIV/AIDS (PLWH), the proportion of adult (≥15 years) PLWH with CD4+ counts <200 cells/μL, and antiretroviral therapy (ART) coverage were obtained from the Thembisa model, version 3.2.[6] Among adult PLWH with CD4+ counts <200 cells/μL, we assumed that half had counts <100 cells/μL based on Carmona *et al.*,[7] who reported that of 654 868 PLWH

Table 1. Population characteristics and underlying comorbidities in South Africans

Population characteristic	*n*	Source
Total population	56 521 947	Statistics South Africa[5]
Women aged 15 - 54 years	16 708 323	Statistics South Africa[5]
Children (<15 years)	16 724 831	Statistics South Africa[5]
Persons living with HIV	7 046 301	Thembisa model[6]
Adults living with HIV + CD4+ <200 cells/μL	676 445	Thembisa model[6]
Adults livings with HIV + CD4+ <350 cells/μL	2 012 674	Thembisa model[6]
Persons living with HIV on ART	372 3118	Thembisa model[6]
Children living with HIV	329 430	Thembisa model[6]
Children living with HIV on ART	181 372	Thembisa model[6]
AIDS deaths	126 755	Statistics South Africa[5]
Annual cases of TB	438 000	World Health Organization[2]
Annual cases of pulmonary TB	394 000	World Health Organization[2]*
Adults with asthma	2 477 539	World Health Survey[10]
Adults with COPD	2 249 688	Global Burden of Disease 2015[9]
Renal transplants per year	249	Organ Donor Foundation[11]
Lung transplants per year	14	Organ Donor Foundation[11]
Heart transplants per year	25	Organ Donor Foundation[11]
Liver transplants per year	35	Organ Donor Foundation[11]
Allogeneic stem cell transplants per year	107	EBMT survey[12]
Persons with lung cancer	7 793	Global Burden of Disease 2015[9]
Persons with acute myelogenous leukaemia	518	Global Burden of Disease 2015[9]
Persons on peritoneal dialysis	1 668	South African Renal Registry[13]
ICU beds	4 719	Naidoo *et al.*, 2013[38]

ART = antiretroviral therapy; TB = tuberculosis; COPD = chronic obstructive pulmonary disease; EBMT = European Society for Blood and Marrow Transplantation; ICU = intensive care unit.
*Adjusted based on assumption that 90% of TB cases are pulmonary.

who entered care in SA in 2016, 32.9% had CD4+ counts <200 cells/μL and 16.8% had counts <100 cells/μL, and Coetzee *et al.*,[8] who reported that among PLWH who had a CD4+ measurement in 2014 - 2015, 20.56% had counts <200 cells/μL and 9.69% had counts <100 cells/μL.[8] National TB data were obtained from the World Health Organization (WHO).[2] National prevalence data for lung cancer and chronic obstructive pulmonary disease (COPD) and incidence data for acute myeloid leukemia (AML) were obtained from the 2016 Global Burden of Disease study.[9] The prevalence of asthma in adults was assumed to be 6.09%, based on the World Health Survey.[10] Transplantation volume was obtained from the Organ Donor Foundation.[11] The number of autologous stem cell transplants in 2014 was obtained from Passweg *et al.*,[12] and the number of end-stage kidney disease patients receiving peritoneal dialysis (PD) in 2015 was reported by the South African Renal Registry.[13]

Assumptions on which we predicated estimates of each mycosis are detailed in Table 2. The burden of cryptococcal meningitis was obtained using national laboratory surveillance data from the National Health Laboratory Service's Group for Enteric, Respiratory and Meningeal Diseases Surveillance in South Africa (GERMS-SA),[14] with a correction of 20% to account for the possibility of undiagnosed cases. We estimated the burden of *Pneumocystis* pneumonia (PCP) in adults and children separately. For adults, we assumed that 10% of PLWH who had CD4+ counts <100 cells/μL were hospitalised each year;[15] and based on the observation from SA that ~10% of PLWH admitted to hospital with WHO danger signs and cough were diagnosed with PCP,[16] we assumed that 5% of hospitalisations among PLWH who had CD4+ counts <100 cells/μL were caused by PCP. We assumed that 21% of childhood pneumonia deaths were attributable to PCP, based on data from Botswana;[17] additionally, we assumed that childhood PCP carried a 40% mortality rate.[18,19] Invasive aspergillosis (IA) was assumed to occur as a complication of other disease states or immunocompromising conditions. IA was assumed to complicate 10% of cases of AML, and an equivalent number of cases among all other non-AML haematological malignancies.[20] IA was assumed to complicate 10% of allogeneic stem cell transplants, 0.5%, 4%, 6%, and 4% of kidney, lung, heart and liver transplants, respectively, based on North American data,[21] and 2.6% of cases of lung cancer, based on Chinese data.[22] IA was additionally assumed to complicate 1.3% of severe acute exacerbations of COPD requiring hospitalisation (which was assumed to affect the most severe decile of patients with this condition).[23] Although IA was implicated in 4% of HIV-related deaths in a study from Italy,[24] similar findings have not been reported in autopsy studies from SA.[25-29] We therefore conservatively estimated that 0.5% of HIV-related deaths were caused by IA. Mucormycosis was assumed to affect 2 per million of the population based on data from Europe.[30,31]

Chronic pulmonary aspergillosis (CPA) was assumed to complicate pulmonary TB with and without cavitary lesions in 22% and 2% of cases, respectively.[32,33] We assumed that 22% of cases of pulmonary TB cavitate. We also assumed that pulmonary TB is the underlying diagnosis in 80% of all CPA cases. Allergic bronchopulmonary aspergillosis (ABPA) was assumed to occur in 2.5% of adult asthmatics, based on SA and international data.[34,35] Severe asthma with fungal sensitisation (SAFS) was estimated to occur in 30% of the most severe decile of asthmatics.[36] Although ABPA is also known to complicate cystic fibrosis, estimates of the prevalence of this disease in SA were unavailable.

The burden of candidaemia was assumed to occur in intensive care unit (ICU) and non-ICU inpatient settings at a ratio of 2:1.[37] We determined the number of ICU beds from a national survey from 2008 to 2009[38] and assumed 90% bed utilisation. The

Table 2. Assumptions on which estimates of mycoses are predicated*

Mycosis	Assumptions	Geographical origin of data informing assumptions†	Reference
Cryptococcal meningitis	Reported surveillance data from NICD, plus 20% correction for missed diagnoses	National	GERMS-SA 2017[14]
Pneumocystis pneumonia	For adults, assumed to cause 5% of all hospitalisations among PLWH with CD4+ <100 cells/μL (10% of whom were assumed to be hospitalised each year) In children, PCP assumed to be attributable for 21% of childhood pneumonia deaths and we assumed that 40% childhood PCP cases were fatal	National + regional	Maartens *et al.*, 2018[16] Meyer-Rath *et al.*, 2013[15] Ansari *et al.*, 2003[17] Zar *et al.*, 2001[18] Morrow *et al.*, 2014[19]
Invasive aspergillosis	Complicates 10% of cases of AML per year and an equivalent number among all other haematological malignancies; complicates 10% of allogeneic HSCT, 0.5% of kidney SOT, 4% of lung SOT, 6% of heart SOT, 4% of liver SOT, and 2.6% of cases of lung cancer; 0.5% of patients dying of HIV; and 1.3% of the worst 10% of COPD patients (usually hospitalised)	International	Lortholary *et al.*, 2011[20] Herbrecht *et al.*, 2012[21] Antinori *et al.*, 2009[24] Karat *et al.*, 2016[25] Martinson *et al.*, 2007[26] Wong *et al.*, 2012[27] Murray *et al.*, 2007[28]
CPA	Complicates 22% of pulmonary TB cases with cavitation and 2% of pulmonary TB cases without cavitation; cavitary disease assumed to comprise 22% of cases of pulmonary TB. Pulmonary TB assumed to underlie 80% of cases of CPA	National + international	Denning *et al.*, 2011[32] Sonnenberg *et al.*, 2000[33]
ABPA	Assumed to affect 2.5% of asthmatic adults	National + international	Benatar *et al.*, 1980[34] Denning *et al.*, 2013[35]
SAFS	Assumed to affect 30% of the most severe decile of asthmatic adults	International	Denning et al., 2014[36]
Candidaemia	Rate of ICU-associated candidaemia in adults in public hospital ICUs is assumed to be equivalent to that reported at Chris Hani Baragwanath Hospital, and assumed to be double that of private hospital ICUs. 90% of ICU beds assumed to be occupied. Ratio of candidaemic episodes in adults receiving care in ICU to non-ICU beds assumed to be 2:1	National + international	Kreusch and Karstaedt, 2013[39] Tshukutsoane and Scribante, 2008[40] Govender *et al.*, 2016[37]
Candida peritonitis	Post-surgical *Candida* peritonitis is half as common as ICU-related candidemia; PD patients assumed to have 1.7 episodes of peritonitis per year, with 3.8% due to *Candida*	National + international	Montravers *et al.*, 2011[41] Okpechi *et al.*, 2012[42] Isla *et al.*, 2014[43]
Oral candidiasis	Among adults, 38% of PLWH with CD4+ <350 cells/μL; for children living with HIV, oral candidiasis assumed to affect 37% not on ART and 5% on ART	National + regional	Arendorf *et al.*, 1998[44] Nanteza *et al.*, 2014[45] Meless *et al.*, 2014[46] Rwenyonyi *et al.*, 2011[48]
Oesophageal candidiasis	20% of PLWH with CD4 <200 cells/μL	International	Smith and Orholm, 1990[49]
Recurrent vulvovaginal candidiasis	~6% of women between 15 and 54 years of age	International	Foxman *et al.*, 2013[53] Denning *et al.*, 2018[79]
Tinea capitis	6% of children <15 years of age	National + regional	Nweze and Eke, 2017[54] Young, 1976[55]
Mucormycosis	2 cases per million population	International	Bitar *et al.*, 2009[31]

NICD = National Institute of Communicable Diseases; GERMS-SA = National Health Laboratory Service Group for Enteric, Respiratory and Meningeal Diseases Surveillance in South Africa; PLWH = persons living with HIV; PCP = *Pneumocystis* pneumonia; AML = acute myelogenous leukaemia; HSCT = haematopoietic stem cell transplantation; SOT = solid organ transplantation; COPD = chronic obstructive pulmonary disease; TB = tuberculosis; CPA = chronic pulmonary aspergillosis; ABPA = allergic bronchopulmonary aspergillosis; SAFS = severe asthma with fungal sensitisation; ICU = intensive care unit; PD = peritoneal dialysis; ART = antiretroviral therapy.
*Estimates for emergomycosis, histoplasmosis, sporotrichosis, blastomycosis, chromoblastomycosis and eumycetoma were based on literature review and the authors' unpublished observations.
†Regional implies another country in sub-Saharan Africa, while international implies outside sub-Saharan Africa.

incidence of ICU-associated candidaemia in public hospital ICUs was extrapolated from cross-sectional data from Soweto.[39,40] We assumed that the rate of candidaemia in private hospital ICUs was half that of public hospital ICUs, based on the assumption of lower general acuity and complexity of private hospital ICU patients that follows from greater accessibility (75% of ICU beds were in the private sector, which provides care for ~15% of the population[38]). We assumed that post-surgical *Candida* peritonitis (intra-abdominal candidiasis) was

half as frequent as ICU-associated candidaemia, as it was in France.[41] In addition, the incidence of *Candida* peritonitis associated with PD was estimated based on the number of PD patients and according to reports of PD-associated peritonitis from Cape Town and Limpopo Province.[42,43] Oral candidiasis was assumed to affect 38% of adult PLWH who had CD4+ counts <350 cells/μL; this estimate was based on a large SA study in the pre-ART era that reported oral candidiasis among 38% of HIV-infected patients,[44] in addition to a study from Uganda that suggested that this opportunistic infection is significantly more likely below this CD4+ threshold.[45] Oral candidiasis was assumed to affect 5% of children living with HIV on ART[46] and 37% of children living with HIV not taking ART,[47,48] based on data from elsewhere in sub-Saharan Africa. Oesophageal candidiasis was assumed to affect 20% of adult PLWH who had CD4+ counts <200 cells/μL, based on a study from Denmark of patients with AIDS;[49] estimates were not attempted for this disease among children. Although vulvovaginal candidiasis occurs more frequently in HIV-infected women than in HIV-uninfected women,[50] most SA studies are cross-sectional and not longitudinal, and therefore do not inform the incidence of recurrence.[50,51] Based on international data,[52,53] we conservatively assumed that recurrent vulvovaginal candidiasis – defined as ≥4 episodes per year – had a prevalence of 6% among females aged 15 - 54 years; this risk was not adjusted for HIV status.

Based on a review of SA and southern African literature, we estimated the prevalence of tinea capitis among children aged <15 years to be 6%.[54,55] Among these, at least 2% and perhaps as many as 14% of cases are complicated, with inflammatory tinea capitis or kerion.[56,57] The incidences of endemic and inoculation mycoses were estimated based on the authors' experience and the published literature.[58-63] We could find no data on fungal keratitis.

Results

In total, we estimated the occurrence of 3 220 014 cases of fungal infections each year (Table 3), with a sensitivity bounds of 2 415 010 - 4 025 017. We estimated 8 357 cases of HIV-associated cryptococcal meningitis each year (14.8/100 000). This disease is rare in children: 3% of cases audited by GERMS-SA were diagnosed in patients aged <15 years.[14] We estimated 1 691 cases of PCP per year in adults (4.3/100 000) and 2 761 cases in children (16.5/100 000), for a total of 4 452 cases per year (7.9/100 000).

We estimated a total of 3 885 cases of IA annually (4.7/100 000), including 3 128 cases among persons with COPD or lung cancers, 576 cases among PLWH and 120 cases among persons with other malignancies or transplant recipients. There were estimated to be 394 000 cases of pulmonary TB per year;[2] it was assumed that 10% of these patients died, leaving an estimated 354 600 survivors. We estimated 22 694 incident cases annually and 71 533 prevalent cases of CPA complicating TB (carrying an annual 15% mortality or surgical resection rate). In total, the prevalent burden of CPA was estimated as 89 416 cases. The burdens of ABPA and SAFS were estimated as 60 591 and 79 980 cases, respectively, although there is likely to be some duplication: some ABPA patients have severe asthma, and all are sensitised to *Aspergillus fumigatus*.

In 2008 - 2009, there were 4 719 critical care beds in SA.[38] Of these, 3 533 (75%) were in private sector hospitals that provide care for ~15% of the population,[64] and 1 186 (25%) were in the public sector.[38] We assumed an occupation rate of 90% of ICU beds across both public and private hospitals. Between 2005 and 2007, there were 49 episodes of candidaemia reported in adult ICU patients at Chris Hani Baragwanath Hospital, a 2 700-bed tertiary hospital in Soweto with an 18-bed ICU,[39] giving a rate of 1.36 episodes of candidaemia per ICU bed per year. If one extrapolates this rate to all occupied public hospital ICU beds and assumes that this rate is halved in private hospital ICUs, it can be calculated that there were 3 614 episodes of candidaemia in adult ICUs. Govender *et al.*[37] noted that two-thirds of episodes of candidaemia occurred in ICU patients in a passive laboratory-based surveillance programme tracking resistance to antifungal drugs in *Candida* species in SA (TRAC-South Africa). We would therefore expect 1 807 episodes in adults outside ICUs for a total of 5 421 episodes of candidaemia per year (9.6/100 000). Reliable data regarding rates of candidaemia in neonatal ICUs could not be found, although Govender *et al.*[37] reported that a quarter of isolates collected in the TRAC-South Africa study were from neonates. If we assume that post-surgical *Candida* peritonitis is half as frequent as candidaemia in ICUs, as it was in France, then 1 807 cases are anticipated. In 2015, 1 668 end-stage kidney disease patients received PD across SA.[13] In a Cape Town cohort of patients receiving PD in 2010, the incidence of peritonitis was 1.7 episodes per patient per year and 3.8% of episodes were caused by fungi.[42] In Limpopo, the incidence of PD-related peritonitis in 2008 was 0.8 episodes per year, also with 3.8% caused by fungi.[43] If we assume an average incidence of PD-related peritonitis of 1.3 episodes per patient per year, with 3.8% caused by *Candida*, then an additional 82 cases of *Candida* peritonitis are anticipated, for a total of 1 901 incident cases of *Candida* peritonitis (3.4 cases/100 000). We estimated 828 666 PLWH with oral candidiasis, including 764 816 adults and 63 850 children. Additionally, we estimated that 135 289 adult PLWH had oesophageal candidiasis. An estimated 1 002 499 women were afflicted by recurrent vulvovaginal candidiasis each year.

Several studies have reported on tinea capitis among children in sub-Saharan Africa.[54] In 1976, Young[55] reported prevalence rates of tinea capitis of 19% and 12% among rural black children in the Northern Transvaal and Eastern Transvaal provinces of SA, respectively, with an overall prevalence of 15%. Using the conservative estimate that 6% of SA children aged <15 years would be affected by tinea capitis, we estimated 1 003 490 such infections. Among these, we estimate the occurrence of at least 20 000 and perhaps as many as 130 000 cases of inflammatory tinea capitis or kerion, a painful and stigmatising disease that can become complicated by permanent hair loss.[56,57]

Dimorphic fungal infections are reported sporadically and are occasionally associated with outbreaks. The recent introduction of molecular typing methods for identification of dimorphic fungi has resulted in recognition of *Emergomyces africanus* (formerly *Emmonsia* sp.) as the most common dimorphic fungus implicated in human disease in SA.[65] In a prospective study of PLWH with CD4+ counts <100 cells/μL and recent-onset, widespread skin lesions (the most common clinical manifestation of disease) who were receiving care at public sector hospitals in Cape Town, 14 cases of emergomycosis were diagnosed in as many months.[58] Among hospitals in Gauteng Province, 10 cases were diagnosed during a 14-month period in 2014 - 2015 at Chris Hani Baragwanath Hospital alone.[66] In Eastern Cape Province, 5 cases were diagnosed in private sector hospitals between 2008 and 2013, but none in public sector hospitals.[67] Assuming that the ratio of public to private sector cases in the Eastern Cape is the same as in the Western Cape (10:1[67]), then an additional 45 public sector cases went undetected during this time. It is likely that many more cases are being misdiagnosed. We therefore estimated 100 cases of emergomycosis per year. Compared with emergomycosis, histoplasmosis appears to be less common in the Western Cape[58] and more common in KwaZulu-Natal.[68] Rarely, outbreaks associated with caving activities have been reported.[69,70] We

Table 3. Estimated burden of fungal diseases in South Africa

Mycosis	Rate, /100 000*	Cases per year, *n**	Sensitivity bounds (lower - upper)
Cryptococcal meningitis	14.8	8 357	6 268 - 10 446
PCP	7.9	4 452	3 339 - 5 565
Invasive aspergillosis	4.8	3 885	2 914 - 4 856
CPA	158.2	89 416	67 062 - 111 770
ABPA	109.6	61 938	46 454 - 77 423
SAFS	131.5	74 326	55 745 - 92 908
Candidaemia	9.6	5 421	4 066 - 6 776
Peritoneal candidiasis	3.4	1 901	1 426 - 2 376
Oral candidiasis	1 466	828 666	621 500 - 1 035 833
Oesophageal candidiasis	239	135 289	101 467 - 169 111
Recurrent vulvovaginal candidiasis†	3 547	1 002 499	751 875 - 1 253 124
Tinea capitis	1 775	1 003 490	752 618 - 1 254 363
Mucormycosis	0.2	113	85 - 141
Emergomycosis	0.2	100	75 - 125
Histoplasmosis	0.1	60	45 - 75
Sporotrichosis	0.07	40	30 - 50
Blastomycosis	0.02	10	8 - 13
Chromoblastomycosis	0.07	40	30 - 50
Eumycetoma	0.02	10	8 - 13
Total	5.7	3 220 014	2 415 010 - 4 025 017

*Rates are presented as cases per 100 000 to enable comparison across countries; however, rates for mycoses largely depend on the underlying condition or demographics, as detailed in the text and in Table 2. Cases are number of people affected in a given year. For some conditions (e.g. CPA, ABPA, SAFS, recurrent vulvovaginal candidiasis and eumycetoma) infections are chronic, and the rate therefore reflects prevalence. For all others, rate reflects incidence.
†Females only.
PCP = *Pneumocystis* pneumonia; CPA = chronic pulmonary aspergillosis; ABPA = allergic bronchopulmonary aspergillosis; SAFS = severe asthma with fungal sensitisation.

estimated the occurrence of 60 cases per year. While blastomycosis is endemic to SA, it is uncommon;[71-74] we estimated 10 cases per year. Sporotrichosis, an implantation mycosis that can also present with pulmonary and disseminated disease in HIV,[58,75] has been implicated in sporadic infections and outbreaks in SA, the latter primarily reported among mineworkers.[59,76,77] We estimated 40 cases of sporotrichosis per year. We respectively estimated 40 cases and 10 cases annually of chromoblastomycosis and eumycetoma, two other implantation mycoses.

A single study of infectious keratitis in Mopani District found 1 of 46 (2.2%) cases to be fungal in aetiology using the less sensitive technique of corneal swabs; a country estimate of fungal keratitis caseload is not possible from these scanty data.[78]

Discussion

SA faces a number of important healthcare challenges, most notably HIV and associated infections including TB, but also antimicrobial-resistant bacterial infections, food-borne outbreaks and non-communicable diseases. Understanding the magnitude of respective problems will be critical for prioritising limited resources, but few national data are available to quantify the burden of fungal diseases in SA. The current study represents an attempt to estimate the burden of these infections, and adds to a growing number of national estimates demonstrating the substantial impact of mycoses.[4] We estimated an annual burden of ~3.2 million cases of fungal diseases in SA (excluding dermatophytes other than tinea capitis), suggesting that these infections cause significant morbidity in this country.

The most frequently encountered diseases, tinea capitis and recurrent vulvovaginal candidiasis, while not life-threatening, are stigmatising and potentially debilitating for those affected. Our estimate of just over 1 million women with recurrent vulvovaginal candidiasis differs slightly from figures reported for SA in a recent global estimate only because of differences in the source data for population estimates; underlying assumptions about the prevalence of recurrent vulvovaginitis on which the estimates were made are similar.[79] We were unable to quantify the incidence of fungal keratitis, a sight-threatening disease.

Some of the fungal diseases discussed here can be difficult to diagnose and are associated with high case-fatality rates. Cryptococcal meningitis is the leading cause of HIV-associated meningitis in southern Africa,[80-82] and a leading cause of death among PLWH. We estimated the occurrence of 8 357 cases of cryptococcal meningitis per year in SA. GERMS-SA identified 6 964 cases of laboratory-confirmed cryptococcosis (excluding cryptococcal antigenaemia),[14] and we inflated this figure by 20% to account for additional cases that we presume have occurred in patients not receiving care or in whom the diagnosis was missed. This figure is considerably lower than that proposed by Rajasingham *et al.*,[83] who estimated the occurrence of 21 400 cases of HIV-associated cryptococcal meningitis annually in SA. Our estimate may have been conservative, but it is based on the assumptions that untreated cryptococcal meningitis is uniformly fatal, that few individuals would die at home without presenting to hospital, and that only few patients with the disease who present *in extremis* would not be appropriately investigated by lumbar puncture. The case fatality rate of a first episode of cryptococcal disease in SA patients was reported to be 37%.[14] Fortunately, roll-out of serum cryptococcal antigen testing among persons with advanced HIV, led by the National Institute for Communicable Diseases (NICD), has enabled the detection and treatment of subclinical disease prior to progression to cryptococcal meningitis. A national programme implementing reflexive serum cryptococcal antigen screening of all HIV-seropositive patients with a CD4+ count <100 cells/μL achieved 95% coverage (276 125 patients) in the first year, with cryptococcal antigenaemia detected in 15 757 patients (5.7%).[84]

The majority of studies that have described the incidence of PCP in sub-Saharan Africa have focused on specific populations of ill patients,[85] making determination of the true incidence challenging. We estimated 4 452 cases of PCP per year, including 1 691 cases in adults and 2 761 in children. Our estimate of the burden of PCP in children required an estimate of the proportion of childhood pneumonias caused by PCP; the most relevant study that we could find was from Botswana prior to the widespread use of ART,[17] and this may have led to an overestimation. It should also be noted that the number of cases proven by microscopy or by molecular testing is anticipated to be considerably fewer than our estimate, given limitations in the availability and the sensitivity of microscopy diagnosis.[86,87] For example, Chiliza *et al*.[87] reported that among adult PLWH hospitalised with suspected PCP at a tertiary hospital in Cape Town, the diagnosis was confirmed in just 55%.

We estimated 5 421 episodes of candidaemia in adults each year. A limitation of our estimate is that it extrapolates from data reported for a single large referral hospital's ICU, which may not reflect the true incidence across the country. For comparison with available surveillance data, the NICD's TRAC-South Africa passive laboratory-based surveillance programme – which included just 11 public sector hospitals and 85 private sector hospitals – reported 2 172 cases of candidaemia over a 19-month period in 2009 and 2010.[37] However, there are at least 544 hospitals in SA,[88] suggesting that our estimate is reasonable. In the TRAC-South Africa surveillance, approximately a quarter of isolates were from neonatal ICUs,[89] and these were not incorporated into our estimates. Whereas *C. albicans* is the predominant *Candida* species involved in candidaemia in most parts of the world,[90] *C. parapsilosis* is the species most commonly implicated in candidaemia in SA, and many isolates are resistant to azole antifungals.[37] The relatively high rate of *C. parapsilosis* is symptomatic of poor infection control procedures and/or limited antimicrobial stewardship, which may be important opportunities to reduce the burden of candidaemia and invasive candidiasis. Another major public health concern is the emergence and spread of *C. auris*, a multidrug-resistant yeast associated with nosocomial transmission, which is increasingly being encountered in SA, particularly in ICUs in private sector hospitals.[91,92] Publication of empirical data collected through GERMS-SA is anticipated to clarify the true incidence of candidaemia in SA (N Govender, NICD, personal communication, December 2018).

We estimated 3 885 cases of IA complicating immunocompromising conditions or lung disease based on adjusted data extrapolated from resource-rich settings. In practice, few cases of IA are diagnosed in SA. The diagnosis of IA can be difficult, and usually relies on bronchoscopy for culture and/or galactomannan; the latter can also be used on serum. In SA, galactomannan testing is not widely available. Moreover, access to bronchoscopy is frequently limited to tertiary hospitals. Some international reports have found high rates of IA on autopsy of patients dying of HIV; for example, in Italy, Antinori *et al*.[24] diagnosed aspergillosis on 4% of postmortem examinations of such patients. However, autopsy studies of HIV-infected patients from SA have not reported this finding.[25-29]

The high number of cases of CPA in SA reflects the high burden of TB, and clearly requires validation. Unfortunately, the key laboratory diagnostic test (*Aspergillus* IgG antibody)[93] is not available in the country, despite its first being described in the 1960s and the development of multiple commercial assays since then.[94,95] With a 50 - 80% 5-year mortality, this diagnostic gap is important to address nationally.

ABPA and SAFS, collectively known as 'fungal asthma', are also relatively common: asthma in adults has been measured at 6%.[10] The estimate of ABPA is based on SA data from 1980 in a referral population of asthmatics.[34] Referral patterns could affect this figure, and there may have been changes over the intervening 38 years. Fungal sensitisation studies are rare in Africa, and in SA limited to sensitivity of infants to *Alternaria* spp.,[96] limiting the reliability of our estimate of the burden of SAFS. Clearly, with >100 000 adults affected (and an unknown number of children), fungal asthma needs to be addressed in SA as it is amenable to antifungal therapy as well as the usual treatments for asthma.[36]

HIV-associated endemic fungal infections such as emergomycosis, histoplasmosis and sometimes sporotrichosis are frequently misdiagnosed, and diagnostic delays are commonly fatal.[58,67] Blastomycosis, which is not typically associated with HIV, is frequently characterised by a protracted course and is commonly misdiagnosed – especially as TB; deaths have been infrequently reported.[63] These and other fungal diseases are not notifiable in SA,[97] so the true incidences are unclear.

Similar attempts have been made to estimate the burden of fungal disease for other countries in sub-Saharan Africa[98-101] and elsewhere.[4] Compared with other countries, SA has high burdens of HIV-associated and TB-associated fungal infections, reflecting the disproportionate size of these dual public health scourges. The proportion of patients affected by CPA is probably the largest in the world at 175.8/100 000. In comparison, TB-associated CPA rates were estimated for both Nigeria and the Democratic Republic of the Congo as 42.9/100 000 in 2011,[32] and more recently for India as 24/100 000.[102] Rajasingham *et al*.[83] estimated the incidence of cryptococcal meningitis across countries with a uniform methodology, and found the largest burden in SA, reflecting the scale of HIV in this country.[83]

Our objective is for the estimates presented here to fill knowledge gaps regarding the burden of fungal disease in SA, pending the availability of empirical data. Robust epidemiological studies with optimal diagnostics are required to clarify the true incidence and prevalence of fungal infections. Importantly, the NICD is currently conducting critical surveillance for some of these infections (including candidaemia and cryptococcal meningitis through GERMS-SA), which will be important for supporting or supplanting some of our estimates. Additionally, careful repeated data collection over years will be important to establish trends, which we have not attempted here.

Many improvements in diagnostics could transform both the quality of current epidemiological data on fungal diseases in SA and patient care. The absence (or near absence) of *Aspergillus* antigen (galactomannan), *Aspergillus* IgG, *Aspergillus* IgE, and *Histoplasma* antigen and antibody testing are the most important gaps. Even direct microscopy for fungi is not available in most hospitals. The quiet revolution and incremental improvements in fungal disease diagnostics over the past two decades have almost bypassed SA, with the one important exception of cryptococcal antigen testing in HIV patients, in which SA is leading the world in terms of screening and case finding. Fortunately, most of the newest and best fungal diagnostic tests are inexpensive (<USD10), and given their critical importance to high-quality care, they should be implemented across the country. In addition, access to effective therapy remains a challenge for many patients. Perhaps foremost among the medications to which access is urgently needed is flucytosine, an over-50-year-old medicine shown to reduce mortality from cryptococcal meningitis compared with alternatives, but which remains inaccessible in SA.[103,104]

Conclusions

Fungal infections cause a high burden of disease in SA and should be considered an important public health concern. The majority of

these diseases are complications of HIV, TB, and/or poverty. While public health investment in the underlying conditions is essential, improving strategies for the prevention, diagnosis and management of fungal diseases can help address the morbidity and mortality associated with these conditions.[105]

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