

Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS

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Objective: Cryptococcal meningitis is one of the most important HIV-related opportunistic infections, especially in the developing world. In order to help develop global strategies and priorities for prevention and treatment, it is important to estimate the burden of cryptococcal meningitis.

Design: Global burden of disease estimation using published studies.

Methods: We used the median incidence rate of available studies in a geographic region to estimate the region-specific cryptococcal meningitis incidence; this was multiplied by the 2007 United Nations Programme on HIV/AIDS HIV population estimate for each region to estimate cryptococcal meningitis cases. To estimate deaths, we assumed a 9% 3-month case-fatality rate among high-income regions, a 55% rate among low-income and middle-income regions, and a 70% rate in sub-Saharan Africa, based on studies published in these areas and expert opinion.

Results: Published incidence ranged from 0.04 to 12% per year among persons with HIV. Sub-Saharan Africa had the highest yearly burden estimate (median incidence 3.2%, 720 000 cases; range, 144 000–1.3 million). Median incidence was lowest in Western and Central Europe and Oceania ($\leq 0.1\%$ each). Globally, approximately 957 900 cases (range, 371 700–1 544 000) of cryptococcal meningitis occur each year, resulting in 624 700 deaths (range, 125 000–1 124 900) by 3 months after infection.

Conclusion: This study, the first attempt to estimate the global burden of cryptococcal meningitis, finds the number of cases and deaths to be very high, with most occurring in sub-Saharan Africa. Further work is needed to better define the scope of the problem and track the epidemiology of this infection, in order to prioritize prevention, diagnosis, and treatment strategies. © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins

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Introduction

Cryptococcal meningitis, a fungal infection caused by *Cryptococcus* spp., is one of the most important HIV-related opportunistic infections. In countries with a high HIV/AIDS prevalence, *Cryptococcus* is one of the most common causes of meningitis overall, more frequent than *Streptococcus pneumoniae* or *Neisseria meningitidis* [1–7]. Following the introduction of combination antiretroviral therapy (ART), the incidence of cryptococcosis has declined substantially in North America and Western Europe [8–11].

Understanding the burden of cryptococcal disease is particularly important for public health officials to adequately plan and prioritize needed resources for disease prevention and control. To better define the burden of cryptococcal meningitis, as it relates to other important diseases, and to understand the need for public health attention to this infection, we reviewed available epidemiological data and estimated the global burden of cryptococcal meningitis among persons living with HIV.

Methods

Cryptococcal meningitis incidence data

We searched the published medical literature in November 2007 for eligible articles, using the search terms ‘HIV’ or ‘AIDS’ and ‘opportunistic infection,’ and limiting to studies published in English during or after 1996. An eligible article was one that utilized a prospective or retrospective cohort study design, was conducted in relatively varied healthcare settings (e.g., hospitalized and outpatient), and reported an incidence among persons with HIV or reported results from which incidence rates among persons with HIV could be calculated.

Our initial literature search yielded 9032 references. From these, we identified 19 studies that met our eligibility criteria [8–10,12–27]. Of the 19 studies, seven were population-based studies of large geographically defined areas [8,12,14,15,26,27]. The remaining 12 were provider-based studies that were not defined by geography [9,13,16–25].

Eleven studies directly reported an estimated incidence and in three [9,13,14] the incidence was determined based on data provided in a figure in the original article. For five population-based studies [8,10,12,15,27], the number of cases was reported but the incidence among persons with HIV was not. For three of these studies [8,12,15], we calculated the incidence rates in these areas using the number of cases reported as a numerator and using an available estimate for the total HIV population as a denominator. In one of these three [15], this numerator was the average yearly number of cases during the years of the

surveillance, and, for the other two, we used the estimate for the final year of the study. For denominators, one study reported an estimate in the text [12], and, in another [15], we used a national surveillance report [28], and in the third [8], we used the 2007 United Nations Programme on HIV/AIDS (UNAIDS) estimate [29]. We excluded the other two population-based studies [10,27], because we were unable to determine the HIV population.

Global HIV population data

The global population of persons living with HIV was taken from the estimate for prevalent cases of HIV among adults and children as reported in the 2007 UNAIDS report (33 200 000 cases) [29,30]. A separate HIV population estimate was taken for each of the UNAIDS regions.

Regional and global estimates

We used the median incidence rate from the available studies of a geographic region, as defined by UNAIDS, to estimate the region-specific cryptococcal meningitis incidence. For regions with no available incidence data, we imputed the rate using the median from a region that is both geographically proximal and similar in economic development. Estimates of cryptococcal meningitis burden for each region i (CM_i) were calculated by multiplying the median incidence rate by the 2007 UNAIDS HIV population estimate for each region [30]. The global burden estimate for cryptococcal meningitis was defined as the sum of all regional estimates.

The range of cases in each region was calculated as ± 1 standard deviation (SD) from the regional estimate, in which the region-specific standard deviation SD_i was defined as $SD_i = \sqrt{(\hat{CV} * CM_i)}$. \hat{CV} was the median coefficient of variation of available region-specific CV_i s, and CM_i was the estimate for cryptococcal meningitis cases in the region i . To determine \hat{CV} , we first calculated the coefficient of variation (CV_i) for each region with at least two available and differing data points using the median incidence and a robust estimate of scale based on the interquartile range. Because region-specific incidences were sparse, we pooled information across regions to estimate a common measure of variability, the median coefficient of variation (\hat{CV}). This median coefficient of variation (\hat{CV}) was then applied to each region to calculate the region-specific SD_i . The estimation of SD_i ignores the variability inherent in the estimate of the HIV counts. The SD for the global estimate was calculated as the square root of the sum of the squared SD_i s.

Estimating case fatality

Because mortality is likely to vary regionally, we estimated deaths by using case-fatality rates from clinical trials conducted in developed and less-developed countries [31,32], by reviewing case series, surveillance reports, and reports on outcomes of cryptococcal meningitis [1,5,10,16,26,31,33–39], and by consulting with clinical

experts (N.G., P.G.P.) in the care and outcomes of cryptococcal meningitis. In regions with primarily developed countries, we assumed a 10-week case-fatality rate of 9% among infected persons. Case fatality was estimated to be 55% in regions with primarily less-developed countries, excluding sub-Saharan Africa, where it was estimated to be 70%.

Results

Incidence reported in all studies ranged from 0.04 to 12% per year (Table 1). At least one eligible study was available from all regions except Eastern Europe and Central Asia; North Africa and Middle East; and the Caribbean. For these three regions, incidence rates were imputed: the rate in Eastern Europe and Central Asia, and North Africa and Middle East, were assumed to be the same as East Asia (1.7% per year). The incidence in the Caribbean was assumed to be the same as Latin America (3.4% per year).

Using these rates, we estimated 957 900 (range, 371 700–1.54 million) cryptococcal meningitis cases occurred in 2006 (Table 1). The region with the highest number of estimated cases was sub-Saharan Africa (720 000 cases; range, 144 000–1.3 million), followed by South and South-east Asia (120 000 cases; range, 24 000–216 000). Oceania (100 cases), Western and Central Europe (500 cases), North Africa and Middle East (6500 cases), and North America (7800 cases) were the regions with the fewest.

On the basis of these estimates and the estimates of case fatality outlined above, approximately 624 725 deaths (range, 124 956–1,124 494) were associated with cryptococcal meningitis (Table 1); Oceania is estimated to have had the fewest (nine deaths), whereas sub-Saharan Africa had the most (504 000; range, 100 800–907 200). When comparing the estimate of deaths in sub-Saharan Africa with other diseases excluding HIV, deaths associated with cryptococcal meningitis are higher than tuberculosis (350 000) and approach the number related to childhood-cluster diseases (pertussis, poliomyelitis, diphtheria, measles, and tetanus, 530 000 deaths combined), diarrheal diseases (708 000), and malaria (1.1 million) (Fig. 1) [40].

Discussion

On the basis of review of available epidemiological data, we estimate a very substantial global burden of cryptococcal meningitis, both in terms of numbers of infections and associated deaths. These estimates will be useful for public health officials in designing and prioritizing efforts to prevent, diagnose, and treat cryptococcal disease.

Table 1. Estimated cryptococcal meningitis cases and deaths among 10 United Nations Programme on HIV/AIDS global regions by using published incidence rates from studies conducted in those regions.

Region	Reported yearly incidence, by study (%) ^d					Median yearly incidence	Coefficient of variation (CV) ^e	HIV prevalence, in 1000s	Estimated yearly cryptococcal meningitis cases (range ^b), in 1000s	Assumed 90-day case fatality (%)	Estimated deaths (range), in 1000s
	a	b	c	d	e						
Sub-Saharan Africa	4.0 [16]	3.2 [21]	0.1 [26]	ND	ND	3.2	0.90	22 500	720 (144.0–1296.0)	70	504.0 (100.8–907.2)
East Asia	1.7 [17]	1.7 [22]	ND	ND	ND	1.7	ND	800	13.6 (2.7–24.5)	9	1.2 (0.2–2.2)
Oceania	0.1 ^b [15]	ND	ND	ND	ND	0.1	ND	75	0.1 (0.0–0.1)	9	0.009 (0.0–0.009)
South and South-east Asia	4.7 [20]	3.0 [18]	1.7 [24]	0.5 ^b [12]	12.0 [19]	3.0	0.74	4000	120 (24.0–216.0)	55	66.0 (13.2–118.8)
Eastern Europe and Central Asia	ND	ND	ND	ND	ND	1.7 ^c	ND	1600	27.2 (5.4–49.0)	55	15.0 (3.0–27.0)
Western and Central Europe	0.1 [13]	0.04 ^b [8]	ND	ND	ND	0.07	0.64	760	0.5 (0.1–1.0)	9	0.045 (0.009–0.09)
North Africa and Middle East	ND	ND	ND	ND	ND	1.7 ^c	ND	380	6.5 (1.3–11.6)	55	3.6 (0.7–6.4)
North America	0.6 [9]	1.5 [23]	0.1 [14]	ND	ND	0.6	1.73	1300	7.8 (1.6–14.0)	9	0.7 (0.1–1.3)
Caribbean	ND	ND	ND	ND	ND	3.4 ^c	ND	230	7.8 (1.6–14.1)	55	4.3 (0.9–7.8)
Latin America	3.4 [25]	ND	ND	ND	ND	3.4	ND	1600	54.4 (10.9–97.9)	55	29.9 (6.0–53.8)
Global	ND	ND	ND	ND	ND	ND	ND	33 200	957.9 (371.7–1544.0)	ND	624.7 (125.0–1124.9)

^aRange calculation for region *i* based on the equation $SDI_i = (\bar{C}V * CMI_i)$, in which $\bar{C}V = 0.8$.

^bCalculated based on available data.

^cNo data available; incidence assumed.

^dData presented as incidence [reference number of study from which value was obtained].

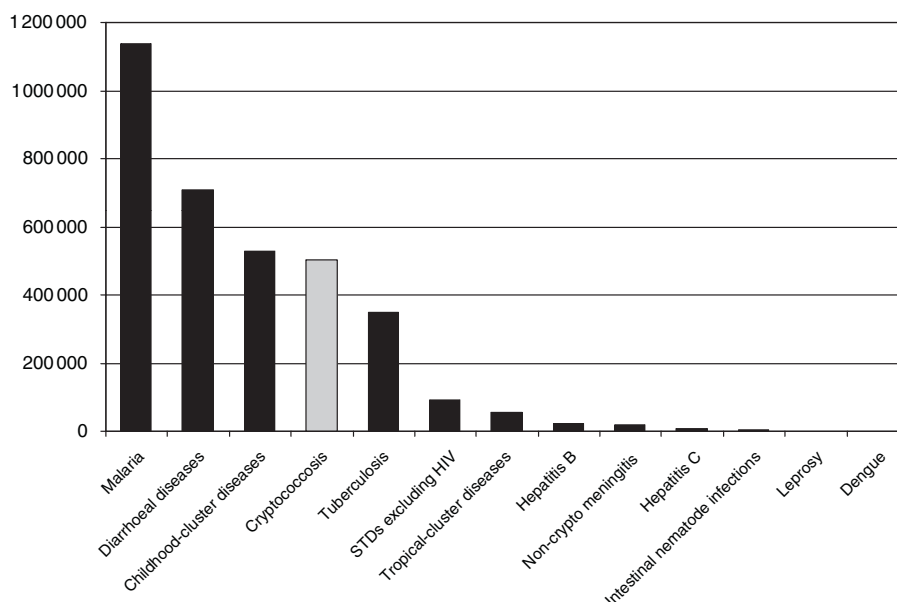


Fig. 1. Comparison of deaths in sub-Saharan Africa due to HIV-related cryptococcosis, as estimated in present study, and common infectious diseases excluding HIV, as estimated by World Health Organization. STD, sexually transmitted disease.

The worldwide number of infections and deaths due to cryptococcal meningitis appear similar to those for diseases that have received greater public health attention. In sub-Saharan Africa, deaths due to cryptococcal meningitis (530 000) may be more frequent than tuberculosis (350 000) [40].

Our estimates of global disease burden are limited by the number of available studies in the literature and by the limitations of the original studies themselves. Provider-based cohort studies may not be representative of the region as a whole, and larger, population-based studies may be limited by incomplete follow-up or case ascertainment. For example, in one of the population-based studies from South Africa, the incidence was much lower than other studies from sub-Saharan Africa, likely due to incomplete case ascertainment [26].

We assumed case-fatality rates based on reviewing reports from clinical trials, surveillance studies, and expert opinion. Despite these assumptions, we feel that the number of deaths is fairly accurate, particularly in sub-Saharan Africa, as our estimate is consistent with what would be calculated from HIV cohort and natural history studies. These studies report that 13–44% of HIV/AIDS deaths are due to *Cryptococcus* [16,38,41]. If 2094 996 HIV/AIDS deaths occur annually in sub-Saharan Africa [40], then annual *Cryptococcus*-related deaths should range from 272 349 to 921 798.

Many of the incidence estimates used here were determined prior to the current effort to provide wide access to antiretroviral treatment. However, as the number of persons still needing antiretroviral drugs is

likely to be stable or even increasing, due to the evolution of the HIV epidemic in many of these areas, expanding access to ART is not likely to impact the global burden of cryptococcal disease soon. In fact, rates of cryptococcal meningitis in South Africa have actually increased since the introduction of antiretroviral therapy [42], thereby emphasizing the growing and future need for attention to this problem.

In many of the developing countries in sub-Saharan Africa and South and South-east Asia, the capacity to perform the complicated management of severe cryptococcal meningitis is limited [43]. An important step in reducing the impact of this infection undoubtedly is the marked expansion of ARV access therapy for HIV, as risk of cryptococcal disease is substantially reduced among persons receiving these treatments. However, because the numbers of people with advanced immunosuppression from HIV and cryptococcal disease will continue to remain high despite expanded access to antiretroviral therapy, specific public health efforts are needed.

One such effort should be the expansion of laboratory diagnostic capacity for cryptococcal meningitis, such as India ink staining of cerebral spinal fluid, and the cryptococcal antigen latex agglutination test, which is simple to use, has high sensitivity and specificity [44], and requires little training for the proper use and interpretation.

Prevention of disease is the ultimate public health goal in the approach to cryptococcal meningitis, though this may be difficult to achieve. Although most clinical trials did not show a survival benefit [45–48], additional clinical

trials are warranted, especially in sub-Saharan Africa, where the incidence of cryptococcal meningitis is high and outcomes of infection are poor. Another strategy that warrants further investigation is screening for early cryptococcal disease with the serum cryptococcal antigen test. Nonmeningeal cryptococcal infection often precedes meningitis but is underrecognized or misdiagnosed [16,35,49–51]. Early detection and treatment of asymptomatic or latent cryptococcal infection may allow for fluconazole to be used as the first-line therapy, a much less expensive and highly available option.

Our findings underscore the tremendous burden of cryptococcal meningitis, as well as the critical need for a better understanding of its epidemiology in developing countries with large numbers of persons living with HIV/AIDS. A focused effort to improve diagnostic capacity, expand treatment options, and identify effective measures for prevention of cryptococcal disease is urgently needed.

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