Epidemiological Trends for Cryptococcosis in Swaziland (Eswatini), Southern Africa

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Abstract

Cryptococcosis is a fungal disease that is characterized by inflammation of the lungs and central nervous system, and it is commonly associated with HIV/AIDS. Even though the disease accounts for roughly 15% of all AIDS-related deaths, it is relatively neglected. This is most especially true in Southern Africa which has the highest HIV/AIDS cases in the world and accounts for more than 10% of all HIV/AIDS cases worldwide most especially in Southern African countries such as Swaziland (Eswatini) which has the highest HIV/AIDS adult prevalence rate in the world. Despite this, there are little or no previous studies with regards to the epidemiological trends for cryptococcosis in Swaziland (Eswatini) which further suggests that it is relatively neglected. With the increasing spread of virulent strains of the fungus such as *Cryptococcus gattii* causing outbreaks in several countries around the world, it is important to have a concrete understanding of the epidemiological trends for cryptococcosis in Swaziland (Eswatini). This is also important during the current coronavirus outbreak as previous studies have reported higher morbidity and mortality rates among COVID-19 patients that are also co-infected with HIV/AIDS, cryptococcus as well as other secondary infections. This is further supported by the fact that Southern Africa has the highest number of COVID-19 cases in Africa as well as one of the highest in the world. As a result, the purpose of this study is to determine the epidemiological trends for cryptococcosis in Swaziland (Eswatini) as this will enable adequate control, management, assessment, policies, and regulations that will be useful during outbreaks. This will be achieved by performing a repeated cross-sectional study to determine the epidemiological changes and trends for cryptococcosis in Swaziland (Eswatini) over a 5-year period from 2023 to 2028.

Keywords

Public Health, Epidemiology, Cryptococcosis, HIV/AIDS, Swaziland

Impact, purpose and statement of need

The purpose of this project is to determine the epidemiological trends for cryptococcosis in Swaziland (Eswatini) over a period of 5 years from 2023 to 2028. This will enable changes in epidemiological trends such as the prevalence of cryptococcosis in Swaziland (Eswatini) to be tracked overtime. There are 5 main reasons as to why this study is needed:

1) HIV/AIDS is commonly associated with cryptococcosis and Swaziland (Eswatini) possesses the highest HIV/AIDS adult prevalence rate in the world.

2) Lack of previous studies regarding the epidemiological trends for cryptococcosis in Swaziland (Eswatini).

3) Follow up and improvement of a current study regarding cryptococcosis in Swaziland (Eswatini).

4) Lack of historical data regarding cryptococcosis in Swaziland (Eswatini) as well as the technology, resources, infrastructure, and policies to routinely screen, detect and diagnose cryptococcosis.

5) Facilitate the development of adequate control, management, assessment, and regulations that will be useful during outbreaks.

Literature review

Cryptococcosis is a fungal disease that is characterized by infection and inflammation of the lungs and central nervous system resulting in pneumonia as well as meningitis that causes brain lesions called cryptococcomas. Infection of the lungs can result in respiratory failure whereas central nervous system infection can lead to tumors within the brain and spinal cord, seizures, hydrocephalus, neurological/cognitive deficits, headache, photophobia and neck stiffness (Centers for Disease Control and Prevention 2018). The disease is mainly caused by the fungus *Cryptococcus neoformans* as well as other similar fungi within the same genus (MacDougall et al. 2007). Cryptococcosis is commonly associated with immunocompromised individuals such as those with HIV/AIDS most especially individuals with a CD4 count < 100 cells/mm^3. It is also the second deadliest secondary infection among individuals with HIV/AIDS most especially for those living in Africa; with tuberculosis being the most deadliest (Nyazika et al. 2018). The disease is relatively neglected and not studied extensively even though it accounts for approximately 15% of all AIDS-related deaths globally (Nyazika et al. 2018). Furthermore, the number of incident cases for cryptococcosis in 2014 was estimated to be 223,100 with 73% of them occurring in sub-Saharan Africa which includes countries in Southern Africa (Nyazika et al. 2018). One of the reasons for this is because Southern Africa accounts for more than 10% of all HIV/AIDS cases worldwide most especially in countries such as Swaziland (Eswatini), Lesotho, Botswana, South Africa, Namibia, Zimbabwe, Zambia, Mozambique and Malawi (

UNAIDS 2019). Out of these countries, Swaziland (Eswatini) has the has the highest HIV/AIDS adult prevalence rate of 27.20% (Central Intelligence Agency 2019). Even though Swaziland (Eswatini) has the highest adult prevalence rate of HIV/AIDS in the world, there has been little or no study with regards to the epidemiological trends for cryptococcosis in Swaziland (Eswatini). A current study that was recently published in 2020 which is also the only primary research study regarding cryptococcosis in Swaziland (Eswatini) found that the prevalence of cryptococcus in 2014/2015 was 8% among HIV/AIDS patients with a CD4 count < 100 cells/mm^3 (Haumba et al. 2020). This rate is significantly higher than the global average of 6% amongst HIV/AIDS patient with CD4 < 100 cell/mm^3 which suggests the need for a follow-up study to determine the epidemiological trends for cryptococcosis in Swaziland (Eswatini) as this will enable changes to be tracked overtime.

Although HIV/AIDS patients and immunocompromised individuals are mostly at risk, it is important to note that the disease can also infect healthy and immunocompetent individuals most especially with virulent strains of the fungus such as *Cryptococcus gattii* which has caused previous outbreaks in countries such as Canada and United States where the prevalence of HIV/AIDS are relatively low (Abbas et al. 2015, Kidd et al. 2004, Ma et al. 2009, MacDougall et al. 2007). Unlike *C. neoformans* which is less virulent and mainly found in sub-Saharan Africa, most cases of *C. gattii* infection occur in Papua New Guinea and Northern Australia as the fungus is endemic and mainly found within that region (Springer et al. 2014). However, previous outbreaks in distant regions such as Canada, the United States, India and Brazil suggest that it is possible for this virulent species to spread to countries in Southern Africa such as Swaziland (Eswatini) making the situation even worse and more difficult to control the disease in a region that already has a high prevalence of HIV/AIDS. As a result, it is important to have a strong understanding of the epidemiological trends for cryptococcosis in Swaziland (Eswatini) especially if an outbreak were to occur. This is also important during the current COVID-19 pandemic as previous studies have reported higher morbidity and mortality rates among COVID-19 patients that are also co-infected with HIV/AIDS, cryptococcus as well as other secondary infections (Bhaskaran et al. 2020, Davies 2020, Geretti et al. 2020, Williamson et al. 2020). Take for instance, a recent study in South Africa by Davies (2020) showed that COVID-19 patients co-infected with HIV/AIDS and other secondary infections such as cryptococcus doubled the risk of mortality. This is further supported by the fact that Southern Africa has the highest number of COVID-19 cases in Africa as well as one of the highest in the world (WHO 2020). As a result of these, it is important to determine the epidemiological trends for cryptococcosis in Swaziland (Eswatini) as this will result in effective management, control, surveillance, assessment, policies and regulations that will be helpful during an epidemic.

Objectives, concept and approach

The main objective of this study is to determine the epidemiological trends for cryptococcosis in Swaziland (Eswatini). The study will be conducted in Swaziland (Eswatini) due to possessing the highest HIV/AIDS adult prevalence rate in the world as well as due to lack of previous studies regarding the epidemiological trends for

cryptococcosis in Swaziland (Eswatini). This will be achieved by conducting a repeated cross-sectional study to determine the epidemiological trends and changes of cryptococcosis in Swaziland (Eswatini) overtime. The hypothesis for this study **(H1)** states that changes in the prevalence of cryptococcosis will be influenced by changes in the epidemiological trends for cryptococcosis in Swaziland (Eswatini).

Predictions and anticipated findings

As previously mentioned in the approach section, the hypothesis of this study **(H1)** states that changes in the prevalence of cryptococcosis will be influenced by changes in the epidemiological trends for cryptococcosis in Swaziland (Eswatini). The reason for this hypothesis is because prevalence is typically affected by several factors such as the incidence, mortality, recovery, immigration, reoccurrence, prevention, risk factors, duration, and survival rate (Arnold et al. 2020, Noordzij et al. 2010). Take for instance, if the prevalence of cryptococcosis were to increase in Swaziland (Eswatini) overtime, it could be due to epidemiological trends and changes in several factors such as increased incidence, reduced mortality and/or reduced recovery etc. **(P1).** Likewise, if the prevalence of cryptococcosis were to decrease overtime, it could be as a result of reduced incidence, increased mortality, increased recovery and/or changes in several other factors that can affect prevalence **(P2)**. If there are no changes in the prevalence of cryptococcosis overtime, then it could be due to lack of changes or a combination of opposing changes in the factors that affect prevalence **(P3)**.

Study designs

Unlike previous studies which collected and analyzed historical qualitative and quantitative epidemiological data as well as historical clinical data on all cases of cryptococcosis that were previously recorded in public and private laboratories, private and public hospitals/ clinics, medical records as well as records from local, state and federal public health agencies, this method is not feasible in Swaziland (Eswatini) because it is a developing, lower middle income country with a small population and economy that currently lacks the technology, resources, infrastructure and policies to routinely screen, detect and diagnose cryptococcosis (Aguiar et al. 2017, Central Intelligence Agency 2020, Chen et al. 2000, Pyrgos et al. 2013). As a result, the method used in this study will be adapted from Haumba et al. (2020); the only currently available primary research study about cryptococcosis in Swaziland (Eswatini).

Unlike Haumba et al. (2020) which conducted a single cross sectional study to better understand the prevalence of cryptococcosis in Swaziland (Eswatini) during 2014/2015 from August 18th, 2014 to March 19th, 2015, the study design for this proposal will be a repeated cross-sectional study as this will enable the results from Haumba et al. (2020) to be followed up, improved upon as well as determine epidemiological trends and changes overtime (Haumba et al. 2015, Haumba et al. 2020). This will be conducted over a period of 5 years from July 1st, 2023 to June 30th, 2028 with yearly intervals between each

timepoints. The use of historical data is not feasible in this case due to lack of availability of historical primary data about cryptococcosis in Swaziland (Eswatini) (except for 2014/2015 due to the Haumba et al. (2015) study) as well as due to the lack of technology, infrastructure and policies to routinely screen, detect and diagnose cryptococcosis as mentioned previously. As a result, the use of a repeated cross sectional to determine epidemiological trends and changes over a 5-year period from 2023 to 2028 is ideal as this will provide adequate opportunity to collect primary data as well as measure both exposures and outcomes at the same time.

After IRB approval as well as receiving written Informed Consent, the following data will be collected/measured from individuals using questionnaires: coded name and medical record number; address; gender; date of birth; date of death (if applicable); ethnic background; date of cryptococcosis clinical symptom presentation (if any); date of cryptococcosis diagnosis (if any); underlying diseases (if any such as HIV/AIDS); source of culture-positive specimens (if any); areas of infection (if any); results of cryptococcal antigen and histology tests; chest radiographs (if available); as well as brain and chest MRIs and CT scans (if available). Survey sampling will span the entire country and will be randomized prior to analyses.

Case definitions

Cases will be included if they possess ≥ 1 of the following 6 clinical features relating to cryptococcosis. Cases that do not fulfill these criteria will be excluded from the study:

· Isolation of *C. neoformans* from an area in the lungs or brain

· Histological identification of C. *neoformans* within biopsy specimens

· A positive histological India ink-stained CSF indicating *C. neoformans*

· Significant cryptococcal antigens (CrAg) within serum, CSF and/or urine

· Cerebral cryptococcomas lesions (≥ 1 cm in diameter) as shown by MRI/CT scans

· Abnormalities within chest radiographs and thoracic CT scans indicating pneumonia such as fluids, and lesions within the lungs.

Statistical analysis and sample size

Quantitative and categorical variables will be analyzed using a chi-squared test, ANOVA or t-test depending on the data being analyzed for statistical significance. For all analysis, a 95% confidence interval will be used and $P < 0.05$ will be considered to be statistically significant. Statistical analyses will be performed using SPSS version 23 and graphs will be constructed using GraphPad Prism version 6. Appropriate sample sizes will be determined by using the online sample size calculator at https://www.surveysystem.com/sscalc.html with a confidence level of 95%.

Dissemination and sharing of the products of research

Informed consent will be requested to permit dissemination of results for research purposes. Information to be disseminated will also be de-identified to maintain confidentiality. Preliminary results from the study will first be presented at seminars and conferences as this will provide the opportunity to inform the public about the progress of the research as well as receive feedback. Afterwards, the results will be published in a peer reviewed journal. Once the publication process is completed, it will then be disseminated to government agencies, funding agencies as well as other stakeholders to be used as reference document for policy development, recommendations for cryptococcosis screening on a national level, recommendations for investment in improved technology, resources and infrastructure as well as facilitate the development of adequate control, management, assessment, and regulations that will be useful during outbreaks.

Evaluation of the project

The success of the proposal will be evaluated based on 5 main criteria as recommended by the National Institute of Health (NIH) which is the main federal agency under the U.S. Department of Health & Human Services that funds medical related research in the United States (National Institute of Health 2016). Ideally, a proposal needs to fulfill all 5 criteria to be considered successful.

Significance criteria: The significance criterion determines the success of the project based on the importance of the study. This includes questions such as whether or not the project addresses an important problem in the field? Also, if the objectives of the project are achieved, how will it improve clinical practice, scientific knowledge or change treatments or preventative interventions?

Investigator criteria: The investigator criterion determines the success of the study based on the credentials, training, and suitability of the researchers. This include questions such as whether or not the researchers have the appropriate experience and training to perform the study? Also, have they demonstrated a record of accomplishments in their respective fields?

Innovation criteria: The innovation criterion determines the success of the proposal based on the novelty of the research. This includes questions such as whether or not the proposal challenges or changes current research, clinical or preventative practices by utilizing novel methodologies or interventions?

Approach criteria: The approach criterion determines the success of the study based on the feasibility of the methodologies to be utilized. This include questions such as whether or not the methodologies and analyses to be employed are reasonable and appropriate for the study?

Environment criteria: The environment criterion determines the success of the proposal by evaluating the overall environment in which the study will be conducted. This includes the availability of institutional support, technology, infrastructure, resources, responsible conduct of research, ethical guidelines as well as socioeconomics.

Budget

The proposed total budget is $10,115 USD which includes both the direct and indirect costs for the study. The total direct cost is $5115 over a 5-year period from July 1st, 2023 to June 30th, 2028. It is estimated and adapted from Smith et al. (2013) with a yearly cost of $1023 that includes costs for screening, diagnosis and treatment of patients with cryptococcosis. The indirect cost includes administrative expenses that are required to fulfil the direct cost of the study such as stipends for researchers, overheads, and utilities. Based on a cost-benefit analysis, the indirect cost is estimated to be approximately equal to the direct cost with a yearly estimate of $1000 which adds up to $5000 over a period of 5 years.

Timeline

July 1st, 2020 – October 31st, 2020: Complete grant proposal

September 1st, 2020 – June 30th, 2023: Submit proposal for funding approval, IRB approval and study preparations

July 1st, 2023 – June 30th, 2024: Interval #1 of repeated cross-sectional study

July 1st, 2024 – June 30th, 2025: Interval #2 of repeated cross-sectional study

July 1st, 2025 – June 30th, 2026: Interval #3 of repeated cross-sectional study

July 1st, 2026 – June 30th, 2027: Interval #4 of repeated cross-sectional study

July 1st, 2027 – June 30th, 2028: Interval #5 of repeated cross-sectional study

July 1st, 2028 – June 30th, 2029: Analyses of results and publication of study

July 1st, 2029 – December 31st, 2029: Dissemination of results to government agencies, funding agencies and other stakeholders

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Grant title

Grant Proposal: Epidemiological Trends for Cryptococcosis in Swaziland (Eswatini), Southern Africa.

Hosting institution

St. George's University School of Medicine (SGUSOM).

Ethics and security

The study methods and protocols will be reviewed by The Swaziland Scientific and Ethics Committee (SEC), the SGU Department of Public Health and Preventive Medicine (DPHPM) Research and Service Committee (RSC) as well as St. George's University's Institutional Review Board (IRB) which is registered with the Office of Human Research Protections (OHRP) in the US Department of Health and Human Services. After approval by the SGU IRB, it is then sent to the Grenada Ministry of Health Research Oversight Committee (ROC) which provides final clearance. In addition to IRB approval, written Informed Consent will also be provided for each participant to further ensure Responsible Conduct of Research (RCR). The informed consent will be drafted to fulfill the criteria within the SGU IRB Informed Consent Checklist. All data collected/measured will be stored within a secure and encrypted database to ensure confidentially and will only be used for research purposes outlined in the Informed Consent. All information will also be collected in a manner that ensures RCR and also minimizes informational bias.

Author contributions

The grant proposal was written by Ibraheem O. Alimi and reviewed by Dr. Emmanuel Keku.

Conflicts of interest

There are no conflicts of interests to declare.

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