Expanded Pulmonary Aspergillosis assessment in patients with Respiratory diseases in Sierra LEone (ePARSLE)

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ABSTRACT

Background: Some patients with apparent pulmonary tuberculosis don't have TB but chronic pulmonary aspergillosis (CPA). A key test to differentiate TB from CPA is the serum *Aspergillus* antibody (IgG and IgM) lateral flow assay. Sierra Leone is among the top 30 high TB burden countries in the world. In our recent study, nearly 50% of patients treated for TB in the national referral hospital in Sierra Leone had smear-negative TB. Despite this and the fact that CPA is one of the main causes of their symptoms, there is limited data on the burden of this disease among patients with respiratory symptoms in Sierra Leone owing to the limited human resource and diagnostic capacity for the detection, management and prevention of these fungal infections.

Objectives: The objective of the study project will be to:

- Determine what proportion of patients with 'smear/Xpert negative' TB or previously treated TB patients who apparently relapse with new symptoms has CPA
- Develop the capacity of healthcare workers (HCWs) on the detection and management of CPA through training and mentorship.

Methods: We will assess the burden of CPA using a cross-sectional design to collect data on the prevalence of CPA at the national referral hospital, TB referral hospital and four regional hospitals in Sierra Leone among 550 adult (≥18 years) patients who presented to the selected hospitals. A total of 26 HCWs will be trained on the diagnosis and management of CPA using a telehealth platform.

Location of the project: National referral hospital (Connaught Hospital), National TB referral hospital (Lakka Government Hospital) and the four regional hospitals in the South, East, North and Northwestern regions.

Ethical considerations: All the data will be collected as part of good clinical practice and stored confidentially.

Conflicts of interest: Nil

Expected timeline: Project timeline is 18 months. The project starts and end dates are March 2024 and September 2025, respectively.

SCIENTIFIC BACKGROUND AND STATE OF THE ART

Although fungal diseases are a major global health problem, their burden in resource-limited countries is largely unknown (Firacative et al., 2020). Recent estimates of the global burden of fungal infections show a substantial burden (Vallabhaneni et al., 2016). However, data on fungal infections in low- and middle-income countries (LMICs) are scarce due to limited human resources and diagnostic capacity to detect, manage, and prevent fungal infections, including chronic pulmonary aspergillosis (CPA).

The WHO annual report on tuberculosis (TB) identifies approximately 45% of pulmonary tuberculosis patients with a clinical diagnosis of tuberculosis (smear/Xpert negative) (WHO 2020). As a result, many people were treated for TB without evidence of the disease. The most common misdiagnosis is CPA, which leads to considerable morbidity and unnecessary mortality.

CPA can mimic TB, can occur during 6 months of TB treatment or can occur after TB, mainly in those who are left with cavities (Ade et al. 2013). A global prevalence estimates of CPA after TB based on 2005 TB data, indicated ~1.2 million people are affected (Denning et al. 2011). A study from Iran found 6% to have CPA in the first episode of TB in the 12 months since diagnosis (Hedayati et al. 2015). Recent studies from Indonesia found that 13% of patients had CPA after 6 months of anti-TB therapy (Setianingrum et al., 2020).

There is no comprehensive estimate in sub-Saharan Africa of the number of mistaken diagnoses of TB, when the diagnosis was actually CPA. A prospective longitudinal study in the North of Uganda found 6.5% of those with a cavity 2-7 years after TB developed CPA each year (Page et

al. 2019). A study from Nigeria found that 19% of smear/Xpert negative people had CPA (Oladele et al. 2017).

Sierra Leone is among the top 30 high TB burden countries in the world with 24,000 cases (298 TB cases per 100,000 population) (WHO 2020). In our recent study, nearly 50% of patients treated for TB in the national referral hospital in Sierra Leone were clinically diagnosed (Lakoh et al. 2019). Despite this and the fact that CPA is probably the main cause of their symptoms, there is limited data on the burden of this disease among patients with respiratory symptoms in Sierra Leone owing to the limited human resource and diagnostic capacity for the detection, management and prevention of these fungal infections.

RESEARCH OBJECTIVES AND SPECIFIC AIMS

The goal of the ePARSLE project is to strengthen the detection and management of CPA among patients with respiratory diseases in the national referral and regional hospitals in Sierra Leone.

Specifically, between March 2024 and September 2025, the project will:

1. Determine what proportion of patients with 'smear/Xpert negative' TB or previously treated TB patients who apparently relapse with new symptoms has CPA. We hypothesize that there is a high prevalence of CPA among patients with 'smear/Xpert negative' TB or previously treated TB patients who apparently relapse with new symptoms. The output for this objective is a manuscript on the prevalence and risk factors for CPA among patients with 'smear/Xpert negative' TB.
2. Develop the capacity of clinicians and laboratory staff on the detection and management of CPA. We will train and mentor clinicians on the detection and management of CPA and train laboratory personnel in all 6 hospitals to undertake *Aspergillus* IgG/IgM lateral flow assay for *Aspergillus* antibody. We hypothesize that the baseline knowledge level of clinicians on CPA is very low, but that will be improved as we implement the ePARSLE project. We will deliver more advanced clinical management with a smaller group of senior clinicians. The outcome is that HCWs who are trained on CPA will be able to demonstrate good knowledge and practice of CPA after at least 50% of the project implementation compared to the baseline.

DESCRIPTION OF THE PROJECT

Design: The ePARSLE project is designed to generate data on the burden of CPA and develop the capacity of HCWs in the national and regional hospitals of Sierra Leone. We will assess the burden of CPA using a cross-sectional study design to collect data on the prevalence of CPA.

Study setting: Sierra Leone is divided into five geographic regions, including Western Area and North, South, Northwest, East and Southern regions. The Western Area is the most populated region of Sierra Leone and includes Freetown (the capital city). According to the 2015 population census, Sierra Leone has a total of 7 million people, of which 22% (1.5 million) resides in the Western Area (GoSL 2015). Sierra Leone's public health system is divided into three levels of care, such as primary, secondary and tertiary care. The national and regional hospitals provide tertiary care. Sierra Leone has 25 public hospitals, 10 of which provide tertiary services. Seven of the tertiary hospitals are in the Western Area among which four are specialized hospitals providing maternity, pediatrics, and psychiatry services. Due to the heterogeneity of patients admitted to these hospitals, they will be excluded from the ePARSLE program.

After consultation with key stakeholders, the project will be implemented in the national referral hospital [Connaught hospital (CH)], the national TB referral hospital [Lakka Government Hospital(LGH)], the Southern regional hospital [Bo Government Hospital (BGH)], the Northern regional hospital [Makeni Government Hospital (MGH)], the Eastern regional hospital [Kenema Government Hospital (KGH)] and Northwestern regional hospital [Portloko Government Hospital (PLGH)], with bed capacities of 300, 100, 200, 201, 250 and 150, respectively. CH is a national referral hospital that is situated in Sierra Leone's capital. It provides tertiary care services. LGH provide TB services mainly and it is best situated for this project. MGH, PLGH, BGH, and KGH are regional hospitals for the North, Northwest, South and Eastern regions, respectively.

Sample size and justification

Objective 1: We will enroll 550 patients across the six hospitals. We used the 19% of CPA in smear/Xpert negative TB patients from a study in Nigeria (Oladele et al. 2017) assessing the burden of CPA. Assuming 95% confidence interval (Z=1.96) and e=5% would yield a minimum sample size of 236 patients. Thus, our proposed sample size of 550 will sufficiently account for attrition, and allow enrolment of post-TB cases who return to care. In line with the existing bed capacity, 137 patients will be recruited at CH, 46 at LGH, 92 each will be recruited at MGH and BGH, 69 at PLGH and 114 at KGH.

Objective 2: We will build the capacity of 24 HCWs who participate in direct patient care using a telehealth platform.

Study population: For the capacity building project, HCWs (i.e., doctors, laboratory personnel and community health officer) providing direct patients care services will be the target population. Adult (≥18 years) patients who presented to the selected hospitals will be the target population for CPA assessment.

Sampling method: The project will be implemented in two phases.

Phase I: Capacity building of healthcare workers on CPA detection and management

The project will build the capacity of HCWs on CPA detection and management and assess their knowledge, attitudes and practice of CPA before and after the project implementation. We will train and mentor clinicians on the detection and management of CPA and train laboratory personnel in all 6 hospitals to undertake *Aspergillus* IgG/IgM lateral flow assay for *Aspergillus* antibody using a telehealth platform.

Phase II: CPA surveillance and follow up of positive patients

During this phase, each hospital will select two clinicians and two laboratory staff from among the trained personnel to detect and manage CPA. Consecutive adults (≥18 years) with respiratory symptoms will be sequentially recruited as they present, until a sample size of 550 patients is achieved (~ 24 weeks). All recruited patients will be assessed at baseline. Demographic and clinical information will be collected from participants using a standardized data collection form and cross-checked with clinical records. Symptoms and chest ray findings will be recorded using the diagnostic algorithm published in 2018 (Hunter et al. 2020).

Blood samples will be collected into EDTA test tubes and centrifuged to generate plasma for the detection *Aspergillus* IgG/IgM using point-of-care immunochromatographic lateral flow assays. Patients with positive results will be evaluated for treatment. A patient will be diagnosed as having CPA if the *Aspergillus* antibody test is positive. All patients with a positive CPA will be followed up for a period of 6 months.

Data collection, management and analysis: All the data will be recorded electronically on a password protected, cloud-based survey tool and exported to excel format. Analysis will be carried out using SPSS version 21.0 (Armonk, NY: IBM Corp). Data will be summarized using measures of central tendency. Odds ratio and logistic regression analysis will be used to assess the potential independent predictors of CPA. The level of significance for all tests will be set at $p< 0.05$ at 95% confidence interval. Kaplan-Meier estimates will be used to compute the survival probability of patients with CAP. Data on KAP of CPA will be graded using a Linkert scale.

Dissemination of findings: The findings of this study will be published in Open Access peer-reviewed journals. We will prepare several educational sessions/talks and social media materials on CPA. Findings will also be presented at national and international conferences.

Timeline of activities for the ePARSLE project: The project is proposed to start with the finalization and submission of the study protocol to the Sierra Leone Ethics and Scientific Review Committee of the Ministry of Health and Sanitation in March 2024. In April 2024, we will recruit and train the research team on the protocol and engage stakeholders on the study. Data collection will start in June 2024 and last for 8 months (until January 2025). The data will be downloaded from the Epicollect to a Microsoft Excel Sheet, clean, coded and analyse in February 2025 and March 2025. We will prepare technical (manuscript) and financial reports and disseminate the findings in April 2025 and August 2025.

SIGNIFICANCE, IMPORTANCE, INNOVATION AND POTENTIAL BENEFIT

The prevention and control of fungal diseases remains a major challenge, especially in resource-poor countries, despite their huge global burden. To improve on this, there is need to prospectively collect up-to-date data to understand the evolving state of fungal infections, including CPA in Sierra Leone. With support from the Global Action For Fungal Infections and the University of Manchester, we recently estimated that 376, 643 people have serious fungal

infections in Sierra Leone. Of this, 6000 have CPA (Lakoh et al. 2021). This informed our decision to pilot a study on CPA at the national referral hospital in Sierra Leone's capital through the PARSLE project. Data from this study reported that 22% of patients previously treated for pulmonary TB have CPA and are being treated with itraconazole monotherapy (Lakoh et al. 2023). A local need, therefore, is to expand the assessment of CPA to regional hospitals and train healthcare workers on its detection and management in the country. This innovative idea informs our decision to apply for the National Science, Technology and Innovation Council (NSTI) of Sierra Leone grants for a medium-scale assessment of CPA and training of healthcare workers in Sierra Leone using a telehealth platform. This grant will help us expand the detection and management of CPA and improve the ability of health care workers to detect and manage CPA.

APPLICABILITY-EXPECTED USES AND FUTURE TECHNOLOGICAL DEVELOPMENT

The simple LDBio *Aspergillus* IgG/IgM lateral flow assay is perfectly suited to all the hospital laboratories in Sierra Leone, which care for patients with TB. However, it is not quantitative and there are some false negatives. An alternative assay would be ideal to pick up false negatives with the LDBio assay and an ELISA would be suitable to run in batches at national referral hospital in Freetown and Premium Medical Services (SL) Limited. Quantitative *Aspergillus* IgG is useful to manage complex patients over long periods of time. Fungal culture is not performed at all in Sierra Leone currently, so substantial training is required, and we envisage that this project will create the platform to transform this situation throughout the country. A recently accepted review found an azole resistance prevalence in African studies in *Aspergillus fumigatus* of 17.1% and 1.3% in environmental and clinical isolates respectively (Amona). There is therefore some urgency to establish the methodology for susceptibility testing of fungi in Sierra Leone.

Using the findings from this study, the future plan is to expand on data generation and analysis of the burden of CPA to districts, faith-based and private hospitals and advocate for the reporting of CPA and other fungal infections in the national integrated disease surveillance and reporting (IDSR) database system. We will build the capacity of the laboratory personnel in the future to conduct high-volume fungal culture from sputum, with identification of *Aspergillus spp*. At Connaught hospital and Premium Medical Services (SL) Limited in Freetown, we will

extend this education to include identification of the common pathogen species complexes of *Aspergillus,* perform quantitative Aspergillus IgG with ELISA and antifungal susceptibility testing of molds. The primary outcome will be enabling laboratory diagnosis of CPA and improved mycology diagnostics for all forms of fungal infections in Freetown.

SUSTAINABILITY PLAN

We prepared this proposal using a public-private partnership with the Ministry of Health's Surveillance Program and Premium Medical Services (SL) Limited. We believe this will help advocate for the institutionalization of the surveillance of CPA in the country. To this we intend to grow mycology laboratory expertise in several hospitals.

Through the collaboration with the Manchester Fungal Infection Group of the University of Manchester and Global Action For Fungal Infections in Switzerland, a larger grant will be sourced in the future for early career researchers in Sierra Leone to pursue higher degrees on fungal disease.

We will disseminate the findings to clinicians, hospital administrators and the general membership of the Sierra Leone Medical and Dental Association to create awareness and understanding about CPA and integrate CPA into the routine health services.

Finally, the telehealth platform will be expanded to provide routine healthcare services where the capacity is not available.

PROJECT GOVERNANCE AND PARTNERSHIP

The project will be implemented by the College of Medicine and Allied Health Sciences, University of Sierra Leone in partnership with the surveillance program of the Ministry of Health of Sierra Leone and Premium Medical Services (SL) Limited in Freetown.

The lead applicant, Dr. Darlinda Jiba, is a Sierra Leonean Internal Medicine Resident who provides Quality Technical Assessment and Capacity Development in infectious diseases in Sierra Leone. As an early career researcher, she has published over 21 papers on PubMed, including those on fungal infections. Dr. Jiba has obtained acceptance to pursue a Masters in

Epidemiology at the London School of Hygiene and Tropical Medicine and will be doing her dissertation under this project.

Dr. Jiba will be supported by Dr. Sulaiman Lakoh who is a lecturer in the University of Sierra Leone and a Consultant Physician and an Infectious Disease Specialist at Connaught Hospital.

Dr. Jiba will also receive support from the Deputy Program Manager of the National Surveillance Program of the Ministry of Health and Mr. Abraham Muhindo, the Medical Microbiologist from Premium Medical Services (SL) Limited. The National Surveillance program is supported by National Technical Working Groups composed of local and international experts. As the applicant has built a strong collaboration with experts from these programs, the ePARSLE project will be strongly supported by this program.

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