1.0 INTRODUCTION

Acute malnutrition remains a public health concern worldwide with no significant changes made in the reduction of numbers of those affected since 2011 (1). The 2019 UNICEF-WHO-The World Bank Group estimates (1) show that approximately 49.6 million children under five were wasted and 16.6 million of these severely wasted. Of concern is the high mortality rate among the severely wasted children who are reported to have an over twelve fold risk of death compared to well-nourished children. Severe infections, diarrhoea, HIV are among the factors that contribute to the increased mortality (2–4). The compromised intestinal function observed in the children with severe acute malnutrition (SAM) may contribute to this increased risk of mortality. Some of the changes in the intestinal mucosa in children with SAM include atrophy of the villi and microvilli, hyperplasia of the crypts of Lieberkün and infiltration of inflammatory cells in the lamina propria (5–7).

Recent studies have indicated intestinal inflammation as one of the risk factors for mortality among children with complicated SAM (3). This intestinal inflammation has been majorly associated with enteropathogens (3,8). The presence of intestinal inflammation also affects intestinal permeability and gut microbiota diversity. Although remarkable improvement such as weight gain has been documented following nutritional rehabilitation for children with SAM, the same cannot be said about change in intestinal function. Some studies have reported only minimal changes in intestinal permeability (7), mucosal atrophy (9,10) and persistent gut microbiota immaturity after nutritional rehabilitation (11). The explanation for the minimal changes still remains unclear. Moreover, interventions such the use of mesalazine (12), hypoallergenic diets (10), vitamin A supplementation have been tested if they can contribute to improved intestinal morphology and function in children with SAM but only minimal or no changes were observed. It is not known whether use of probiotics could contribute to changes in the intestinal function in children with SAM (13). Probiotics have been shown to improve gut health in well-nourished children and reduce frequency of diarrhoea (14). Probiotics are live organisms when ingested in appropriate quantities confer health benefits including restoration of the normal gut bacteria.

In an effort to improve assessments of gut status and function, recent studies have evaluated the use of simple, reliable and non-invasive fecal and blood biomarkers (15–17). Biomarkers are biomolecules ranging from proteins, lipids, carbohydrates, genes, DNA, RNA, enzymes and hormones that can be measured objectively and used to identify a disease or monitor
progress of a therapeutic intervention. Limited data is available on the use of these biomarkers among children hospitalized with SAM. Over several years, intestinal biopsies have been the gold standard method of assessment of the intestinal mucosa in children with SAM providing accurate information on morphology however it is also a rather invasive procedure. Due to this, assessments of the gut have taken on small sample sizes during research and often there is difficulty in obtaining biopsies from healthy controls. Additionally, obtaining intestinal biopsies requires highly skilled technical capacity that may not be readily available in resource limited settings (5,9). The use of biomarkers may enable researchers get a better understanding of the status of the gut in critically ill children with SAM and monitor the changes in gut status and function during nutritional rehabilitation with minimal discomfort to the child.

We assessed gut function in children hospitalized for SAM during in-patient and out-patient phases of treatment using blood and fecal biomarkers and evaluated the predictors of change of gut function during nutritional rehabilitation. We also assessed one of the approaches for direct transition from F-75 to RUTF during nutritional rehabilitation.

**Objective of the PhD thesis**

1. To describe the gut function of children hospitalized with complicated SAM using blood and fecal biomarkers and assess the correlates of impaired gut function (paper 1).
2. To determine the predictors of change in blood and fecal biomarkers of gut function among children treated for severe acute malnutrition during the in-patient and out-patient phases of nutritional rehabilitation (paper 2)
3. To describe the transition from F-75 to RUTF therapeutic feed, using the first approach by first providing half of the energy requirements from RUTF and the other half from F-75 and then increasing gradually to RUTF as the only energy source during nutritional rehabilitation for children aged 6-59 months with complicated SAM and evaluate the correlates of failed transition to RUTF (paper 3)