INDIVIDUAL AND PUBLIC HEALTH RISKS AND BENEFITS OF THE ROUTINE USE OF AMOXICILLIN IN THE TREATMENT OF SEVERE ACUTE MALNUTRITION (SAM) IN AMBULATORY SETTINGS IN SUB SAHARAN AFRICA

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ERNA RIJNIERSE

KIT (ROYAL TROPICAL INSTITUTE)

VRIJE UNIVERSITEIT AMSTERDAM (VU)

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A thesis submitted in partial fulfilment of the requirement for the degree of

Master of Science in International Health

By Erna Rijnierse

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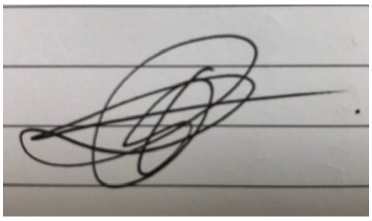

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I. LIST OF ABBREVIATIONS AND ACRONYMS:

AHR	Adjusted Hazard Ratio
AIDS	Acquired Immune Deficiency Syndrome
AMR	AntiMicrobial Resistance
AOR	Adjusted Odds Ratio
ASU	Antibiotics Smart Use
ATFC	Ambulatory Therapeutic Feeding Centre
CI	Confidence interval
CHAIN	Childhood Acute Illness and Nutrition
CMAM	Community- Based Management of Acute Malnutrition
EHP	Essential Health Package
ESBL	Extended-Spectrum Bèta-Lactamase
ESBL-E	Extended-Spectrum Bèta-Lactamase enterobacteria
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HC	Health Centre
HIV	Human Immunodeficiency Virus
HP	Health Post
IMCI	Integrated Management of Childhood Illness
IPC	Infection Prevention and Control
LMIC	Low and Middle Income Countries
MAM	Moderate Acute Malnutrition
MDR	Multi Drug resistant
MSF	Médecins Sans Frontières
MUAC	Mid Upper Arm Circumference
NA	Not Available
OR	Odds Ratio
PICO	Patient Intervention Comparison Outcome
SAM	Severe Acute Malnutrition
SSA	Sub Saharan Africa
RCT	Randomised Controlled Trial
RDT	Rapid Diagnostic Test
RR	Risk Ratio
RUTF	Ready to Use Therapeutic Food
TB	Tuberculosis
UNICEF	United Nations Children Emergency Fund
WASH	Water Sanitation and Hygiene
WHO	World Health Organisation

II. ABSTRACT:

TITLE: Individual and public health risks and benefits of the routine use of amoxicillin in the treatment of Severe Acute Malnutrition (SAM) in ambulatory settings in Sub Saharan Africa

BACKGROUND: About 47 million children under five worldwide are acutely malnourished; 14.3 million of them suffer from severe acute malnutrition (SAM). So far, all children with uncomplicated SAM routinely receive a course of antibiotics when starting treatment. Evidence supporting routine antibiotic use at admission to a nutritional ambulatory treatment programme remains limited. Many studies show that any unnecessary use of antibiotics is a risk for antimicrobial resistance. This thesis studies the pros and cons for the systematic use of antibiotics in children with uncomplicated SAM in ambulatory feeding programmes in Sub Saharan Africa in the light of the emerging antimicrobial resistance.

METHODS: This thesis encompasses a literature review, expert consultation and reviews of the systematic use of antibiotics in the treatment of SAM from different angles and from various perspectives: caregivers, health workers and health systems. The literature review is done using the Vrije Universiteit library, PubMed on relevant trials on antibiotics and SAM, contextual information on the areas of those trials, factors that lead to antimicrobial resistance. Data were searched in period from 2010 till now. In addition, websites from WHO and NGOs were searched for relevant data and documents. The data are triangulated with expert interviews from the field of malnutrition and antimicrobial resistance. The framework used is based on the Antibiotics Smart Use model and includes social determinants of health, which could potentially play a role in the development of antimicrobial resistance.

RESULTS: Two out of six single studies showed no significant difference in recovery rates. However, in one trial there was a difference in referral rates: more referrals in group without antibiotics. The quality of the other study showing no difference was low. Four studies (one RCT and 4 retrospective studies) showed a better outcome with antibiotics. A meta-analysis found a small big significant difference in favour of using amoxicillin: combined RR 1.03, 95% CI [1.00–1.06], p = 0.03).

Reliable data on antimicrobial resistance (AMR) are often not available in the contexts where malnutrition rates are high. Acquisition of AMR is described in hospital settings only so far, no information on acquisition of AMR in ambulatory feeding programs has been published. Acquisition of AMR bacteria in the group of children with severe acute malnutrition that received amoxicillin was significantly higher (53.7% versus 32.2%, adjusted RR = 2.29, P = 0.001) than in the placebo group. Moreover, the same goes for their siblings, who did not take antibiotics. Risk factors for antimicrobial resistance are overuse of antibiotics, not properly using them and poor infection prevention and control. All but one expert believe systematic antibiotics should be continued. While all experts agreed that many children do probably not need antibiotics, there is currently no way on how to detect and decide who does not need them.

CONCLUSION: Based on the current context in sub–Saharan Africa and the current evidence, systematic antibiotics are needed for SAM children in ambulatory settings, despite potential risk on increased AMR. Not using antibiotics may increase the risk of hospital admission, resulting in an increased risk of AMR as well, on top of an increased risk of a poor outcome of the child's health.

KEY WORDS: Severe acute malnutrition, antibiotics, antimicrobial resistance, determinants

WORDCOUNT: 10853

1. INTRODUCTION

About 47 million children under five worldwide are acutely malnourished; 14.3 million of them suffer from severe acute malnutrition (SAM). Malnutrition, in its various forms, can have short-term and long-term health implications(1). Malnourished children are at increased risk of dying from infectious diseases, and malnutrition is believed to be an underlying cause for 45% of under-5 deaths worldwide(2).

Until ready to use therapeutic food (RUTF) which can be administered at household level became available, all children with SAM were admitted in a hospital or inpatient feeding centre. Nowadays, a differentiation is made between children with complicated SAM, which refers to the children who present with SAM with (severe) medical complications needing inpatient care, and children who do not have any apparent medical complications (uncomplicated SAM). These children do not require hospitalisation and are admitted in an out-patient feeding programme, in which the children are provided with therapeutic food to take home (to be given by the caregivers). Every week the patient gets a medical checkup, a new supply of therapeutic food and health education. Currently, as part of the medical treatment, all children with uncomplicated SAM receive a course of oral amoxicillin (a broad-spectrum antibiotic) for five days for, as per World Health Organization (WHO) guidelines (3).

Community based treatment of SAM is very effective, but evidence supporting the routine antibiotic use at admission in ambulatory settings remains limited. In many cases the full course of antibiotics is not completed and is stored for later use by a family member. This potentially increases the risk of antimicrobial resistance (AMR). In view of the costs and consequences of emerging resistance associated with routine antibiotic use, more evidence is required to support this practice of systematic prescription (4).

The WHO (2021) states: 'Providing antibiotics to children with uncomplicated severe acute malnutrition is unlikely to cause them harm, e.g., anaphylaxis or other hypersensitivities. It may, however, contribute to antimicrobial resistance (AMR) in the community"(5). In addition, in the light of the emerging AMR the WHO does recommend to monitor resistance patterns in populations where broad-spectrum antibiotics are recommended for community treatment of severe conditions such as fast breathing (is pneumonia) in the Integrated Management of Childhood Illness (IMCI) programs. This is a system used for community health workers, based on symptomatology, in which lower-trained staff is trained to diagnose and treat diseases in children (6).

Bacterial- or antimicrobial resistance means that bacteria changes in a way that the drugs that used to treat them become no longer effective. This has become a very important public health threat (7). A review on AMR by the United Kingdom Government has indications that AMR could kill yearly about 10 million by 2050 (8).

Antimicrobial resistance is being increasingly reported in countries where SAM is common. This includes the risk of resistance in gram-negative organisms, in particular with increasing rates of extended-spectrum bèta-lactamase (ESBL) producing bacteria (9). This means that antibiotics that are currently used in children with SAM can become not effective. AMR can develop in the gut, when exposed to antibiotics such as amoxicillin, and can cause secondary infections which can be more virulent and more difficult to treat. This could complicate the treatment for SAM children (10).

From a public health perspective, one could argue, that global protocols prescribing systematic antibiotics in SAM children could lead to an increased burden of widespread antimicrobial resistance in the community. At the same time, the benefits for blind systematic use for all children with SAM, including the ones with no medical complications by all health care providers have not been properly established.

Understanding when the use of systematic antibiotics outweighs the risks for the patient could guide programmatic approaches of the ambulatory treatment of children with SAM.

1.1 BACKGROUND INFORMATION:

1.1.1 GEOGRAPHICAL AREA

The area in Afrika beneath the Sahara is commonly referred to as Sub Saharan Africa. It is a very vast and large area, consisting of 48 countries with different climates, cultures, religions and people. Most of the countries are classified as low- and a few as middle-income countries where many projects of Médecins Sans Frontières (MSF) are situated. 18 of the countries are in the top 25 of the fragile state index 2021 (1).

Despite the differences the major health problems and demography in the various countries are remarkably similar:

- A large part of the population consists of young children (17 percent is under five years of age).
- The lowest life-expectancies in the world are found in this area.
- The leading causes of death among children are neonatal deaths, lower respiratory tract infections and diarrhoeal disease.
- The number of healthcare workers per capita is lowest in the world.
- Maternal mortality is still very high even when some improvements have been made.
- Vaccination coverage is lower than in other parts of the world.
- Rates of malnutrition are very high (2).

It is challenging to get reliant data on the epidemiology of malnutrition, as there are methodological challenges as well as contextual factors. Malnutrition follows a seasonal trend, whereby the number of cases sharply rise at time of the pre-harvest rains. This is when food is scarce and generally the incidence of infectious diseases rises and when diarrhoeal diseases and malaria become more frequent. In many cases, the combination of food insecurity (a lack of access to enough qualitative, affordable and nutritious food), as well as displacement population and drought can potentially create conditions leading to famine. Hence in order to provide an estimate, figures from the WHO, UNICEF and World Bank Group Interagency estimates are being used. They provide levels and trends for both growth and malnutrition of children, based on standard anthropometric indices (3).

There are large numbers of cases of SAM present in Sub Saharan Africa. The causes of SAM may differ along and even within the countries. Poverty, conflict and displacement are all factors that can contribute to the development of malnutrition. Even so, the protocol for the treatment of SAM is similar in all countries.

1.1.2 MALNUTRITION

Malnutrition is a term used to describe imbalances, deficiencies or excesses, in intake of energy and/or nutrients, resulting in:

A. under-nutrition: wasting (low weight-for-height, often indicating recent and severe loss of weight, due to illness or not having enough food), stunting (low height-for-age, indicative of more chronic or recurrent low intake and is associated with poverty and poor health of entire families) and underweight (low weight-for-age);
B. micronutrient-related malnutrition, micronutrient deficiency or excess;
C. overweight, obesity and noncommunicable diseases (such as cardiovascular diseases and diabetes) (3).

In this thesis the focus will be on acute malnutrition that is characterised as low weight for height (wasting) or thin arms (measured with Mid Upper Arm Circumference (MUAC)) and or bilateral pitting oedema. Other signs such as changes in skin (desquamation of the skin, destroying the natural barrier and increasing risk of infection) and hair as well as an enlarged liver can be present. The group of children who present with both severe wasting and kwashiorkor (nutritional oedema) are often very ill and thus are at higher risk of dying (11).

Acute malnutrition (or wasting), is a fast deterioration in nutritional status in a short time. In children it is diagnosed by using the weight-for-height or with Mid-Upper-Arm Circumference (MUAC), or the presence of bilateral pitting oedema. There are different levels of severity of acute malnutrition: moderate acute malnutrition (MAM) and severe acute malnutrition (SAM)

Severe Acute Malnutrition (SAM) is defined in children aged six–59 months old as weight-for-height Z-score of <-3 standard deviations of the WHO standards and/or bilateral pitting oedema and/or MUAC <11.5 cm. Z score is defined as the number of standard deviations below or above the reference median value(7) (12).

1.1.3 WHY THE USE OF SYSTEMATIC ANTIBIOTICS IN SEVERELY MALNOURISHED CHILDREN

In the textbooks on nutrition in the 1950's, there was hardly any mention of infections, as the importance of the relationship between infections and malnutrition was poorly understood. Over the years, more became known and understood on the relationship between poor nutritional status. Poor nutrition increases susceptibility to infections, which decreases immunological and metabolic responses, leading again to deterioration of the nutritional status. (13). This means that malnutrition decreases immunity and illnesses increase risk on malnutrition.

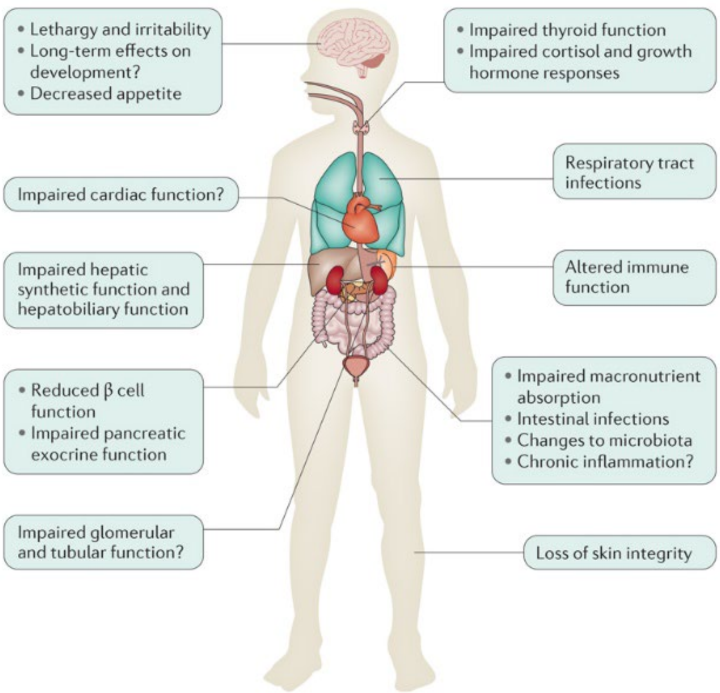

Figure 1: pathophysiology of malnutrition (from (7)*)*

The diagnosis of infection in children with SAM is difficult because typical signs of infection, such as fever, may not be present and the child may present with atypical symptoms like apathy, hypoglycaemia, drowsiness, hypothermia. Many children present with lower respiratory tract- and skin infections (7). In addition, the risk on sepsis increases as bacteria from the colon may colonise the small intestine (referred to as bacterial overgrowth). This is the reason why a systematic course of broad-spectrum antibiotics is prescribed: the diagnosis is difficult, whereas the potential consequences of not prescribing antibiotics are quite serious, potentially lethal (14). Even 50 years after the introduction of systematic antibiotics by the WHO children without apparent metabolic stress still get antibiotics routinely prescribed.

1.1.4 ANTIMICROBIAL RESISTANCE IN CHILDREN IN SUB-SAHARAN AFRICA

Antimicrobial resistance is a growing threat to public health worldwide, especially for young children. The emerging resistance makes the normally used antibiotics not effective, resulting in an increased burden of disease and mortality. In 2019 4.95 million (3.62–6.57) deaths were associated with bacterial AMR and 1.27 million (95% Confidence Interval (CI) 0.911–1.71) deaths were attributed to bacterial AMR. The highest rate in the world was found in western Sub-Saharan Africa with an estimated 27.3 deaths per 100 000 (20.9 – 35.3) (15).

"Children in sub-Saharan Africa are 58 times more likely than those in high-income countries to die of AMR." The number of people who die of AMR is higher than the number of people dying from HIV / AIDS and about twice as high as the number of malaria deaths (16).

The surveillance of AMR in SSA is not consistent due to lack of reliable data, a lack of microbiologic diagnostic laboratories and low quality of these laboratories. Besides this, SSA does not have good strategies to do surveillance in antimicrobials, lacks quality insurance programmes and programmes for infection prevention and control (IPC) are not well established (17).

A high burden of diseases such as respiratory tract infections, parasitic diseases, diarrhoeal diseases, human immunodeficiency virus (HIV) and tuberculosis (TB) is present in the area, for which antibiotics are being prescribed. In many places antibiotics can be bought on local markets and are being randomly used. Health workers have been trained to treat clinical syndromes, which are sensitive in order to capture serious infections, thus resulting in over-diagnosing bacterial diseases and over-prescription of antibiotics, which is an important factor leading to increasing resistance.

Besides, the rising number of infections with multidrug-resistant (MDR) organisms as well as the extended-spectrum β-lactamases producing bacteria (ESBL) in populations (both on community level as well as in hospital level) in Sub Saharan Africa could lead to decreased available suitable antibiotics to be able to treat these infections. Increased resistance will also lead to more use of third- or fourth line antibiotics without the laboratory support or the advice of experts (18).

Studies on AMR often use presence of ESBL bacteria (Extended Spectrum Beta-Lactamase) bacteria as a measurement of antimicrobial resistance. These bacteria (for instance Klebsiella or Escherichia coli) are resistant to penicillin and to cephalosporin, important and frequently used antibiotics.

Most of the AMR originates in hospitals. However, AMR are becoming more common in communities. Facilitating factors for resistance development include behavioural factors and policy or environmental factors. Examples of behavioural factors are: inappropriate infection prevention and control (IPC) measures and inappropriate use of antibiotics. Other factors include the selling and purchasing of antibiotics in local markets, the use of antibiotics for the wrong indications and pressure from patient on the health workers to prescribe antibiotics when they do not really need them (19).

AMR leads to longer duration of illnesses and it is more difficult and costly to treat resistant infections. There are higher mortality rates in patients with resistant infections (20).

AMR is a serious public health risk: To what extend does the systematic provision of antibiotics to non-complicated SAM contribute to this problem? AMR is a risk for the patient, as well as on a public health level as AMR makes the antibiotics less effective leading to loss of lives world-wide.

2 PROBLEM STATEMENT AND JUSTIFICATION

About 47 million children under five worldwide are acutely malnourished; 14.3 million of them suffer from severe acute malnutrition (SAM). In the current situation, all the children aged six months to five years who are admitted in an ambulatory nutritional treatment centre receive a standard course of antibiotics, mostly amoxicillin, along with their nutritional treatment. Even when the WHO recommends a routine prescription of antibiotics, there still is no current consensus (between experts) nor conclusive evidence on whether the routine use of antibiotics is more of a risk or a benefit in the treatment of children with non-complicated severe acute malnutrition in Sub Saharan Africa. Within the WHO and humanitarian organizations such as Médecins Sans Frontières (MSF) doubt has been raised on whether the systematic use of antibiotics is still valid over 50 years since its introduction. Besides, different studies seem to yield different results.

AMR is rising world-wide. It is particularly problematic in LMIC's where diagnostic and treatment options against resistant organisms are limited (21). AMR is causing increasing risks for both individual patient and population.

There are good reasons to limit unnecessary use of antibiotics . The routine inclusion of antibiotics as part of SAM treatment increases cost and complexity. Any simplification or cost-reduction in the feeding protocol (without decreased recovery rates) could expand capacity to provide home-based care for malnutrition for more children in more areas. Additionally, AMR is rising world-wide. It is particularly problematic in LMIC's where treatment options against resistant organisms are more limited(16). Resistant organisms develop in the gut when exposed to broad-spectrum antibiotics such as amoxicillin, causing secondary infections that are difficult to treat. Moreover, resistant bacteria can exhibit enhanced virulence(17), that could complicate chances for recovery for children with SAM.

The problem of severe acute malnutrition is a global one and there is a big burden of disease caused by malnutrition. At the same time, the growing burden of antimicrobial resistance is a big concern for the population worldwide and demands a critical review on the systemic use of antibiotics in outpatient treatment of SAM, especially if not always indicated.

Organisations like MSF wonder if systematic antibiotics should be administered in all situations, or whether the protocol can be applied depending the context. This research envisages to review existing evidence taking contextual factors into account in order to generate a more complete overview of the risk – benefit balance of the systematic use of antibiotics in outpatient treatment of SAM.

2.1.1. RESEARCH QUESTION

What are individual and public health risks and benefits of the routine use of amoxicillin in the treatment of Severe Acute Malnutrition in ambulatory settings in Sub Saharan Africa?

2.1.2. OBJECTIVE

To identify the individual and public health risks and benefits of the routine use of amoxicillin in the treatment of Severe Acute Malnutrition in ambulatory settings in Sub Saharan Africa.

2.1.3. SUB-OBJECTIVES

1. Identify relevant research on systematic use of antibiotics in children with uncomplicated severe acute malnutrition in Sub Saharan Africa.
2. Identify and add contextual information to the outcomes specified on locations of trials.
3. Identify factors that influence antimicrobial resistance (+/-) in Sub Saharan Africa.
4. Identify factors and situations in which prescription is more beneficial, balancing AMR and individual risks and make recommendations accordingly.

3. METHODOLOGY

This thesis envisages to review the systematic use of antibiotics in the treatment of SAM from different angles, and from various perspectives: care-givers, health workers and health systems. It encompasses a literature review and an expert consultation.

3.1 LITERATURE REVIEW

To identify relevant research on the effect of systematic antibiotics in children with uncomplicated SAM, a PICO system will be used:

Table 1: Pico

P	Patient	Uncomplicated SAM case in Sub Saharan Africa
I	Intervention	Systematic antibiotics
C	Comparison	No systematic antibiotics (no antibiotics or prescription only)
O	Outcome	Outcome for patients Indicators of antimicrobial resistance: public health outcome (There is outcome for patient health as well as public health as one could translate reduction in risk of AMR as beneficial for public health)

Included: studies from 2010, comparing antibiotics versus no antibiotics in uncomplicated SAM.

Excluded: studies on complicated SAM, moderate acute malnutrition (MAM) and injectable treatments.

Identification of literature was done by electronic search of data in databases using Google scholar, PubMed, and Vrije University library. Search terms are available in annex 1. Further, related articles were searched by using 'snow balling technique' from the bibliography of the selected articles. The articles are all in English language.

To identify factors influencing AMR a search was done using search terms in various combinations. When no literature on the AMR in geographical context was found, the search got broadened to other countries.

To identify contextual factors, the areas of the studies were looked into. When no information was found in the studies themselves, the search was broadened to other studies in the countries.

Additional: Comprehensive search of websites and official webpages of United Nations, World Health Organization (WHO), United Nations Children Emergency Fund (UNICEF) and MSF were performed for relevant data and documents.

3.2 EXPERT CONSULTATION

As research is limited in reporting on contextual factors, such as AMR, disease patterns and social context, semi-structured interviews are held with experts in nutrition, antimicrobial resistance and advisors from a non-governmental organisation. The aim was to consult experts on their opinion on the use of systematic antibiotics, in relation to contextual factors or circumstances and in the light of the risk of developing AMR.

The participants selected and willing and able to participate were:
two authors: one on a review article, the other author of one of the random controlled trials. In addition, two paediatric advisors from MSF, experienced in nutrition and emergencies participated. Also, the Antimicrobial Resistance Strategic Lead & Policy Advisor MSF and a technical officer from WHO and an Expert in nutrition, member of Childhood Acute Illness and Nutrition (CHAIN) network were also willing to participate. The technical officer from WHO contributes on her own behalf, not in function of WHO.

The research is granted exemption from full ethical review by the Research Ethics Committee. Principles of Helsinki are respected: participants are involved in their professional capacity only, signed informed consent before the data collection, voluntary and informed participation in the interviews.

Prior to the interview, questions were sent to them to allow preparation time. The interviews were recorded and the answers summarised and reported according to the framework components. The interviews are transcribed and sent to the participants for their approval.

A copy of the consent form is available in Annex 4 and the questionnaire is available in Annex 5.

3.3 THEORETICAL FRAMEWORK

Analysis of literature will be done in the light of the selected framework, in which the three levels of interest: individual, community and health systems (see figure 2 below).

The model " Antibiotic Smart Use (ASU)" was used to identify the different categories of risks of systematic use of antibiotics (22) (Model in Annex 2). This model identifies factors for promotion and implementation of rational prescription of antibiotics. It was adapted to fit the purpose of this thesis. The phases of implementation were removed, as they are of no relevance for this thesis.

The outcome in the framework was originally described as patient health only. To fit the purpose, it is now expressed patient health as well as public health: increased risks for AMR. Figure 2 shows the adapted framework

The rational prescription of antibiotics (supply side) by the health workers is influenced by various factors, mostly organisational, network and policy. The uptake of antibiotics is also influenced by various factors, including sharing resources and pressure to take drugs, even when not needed.

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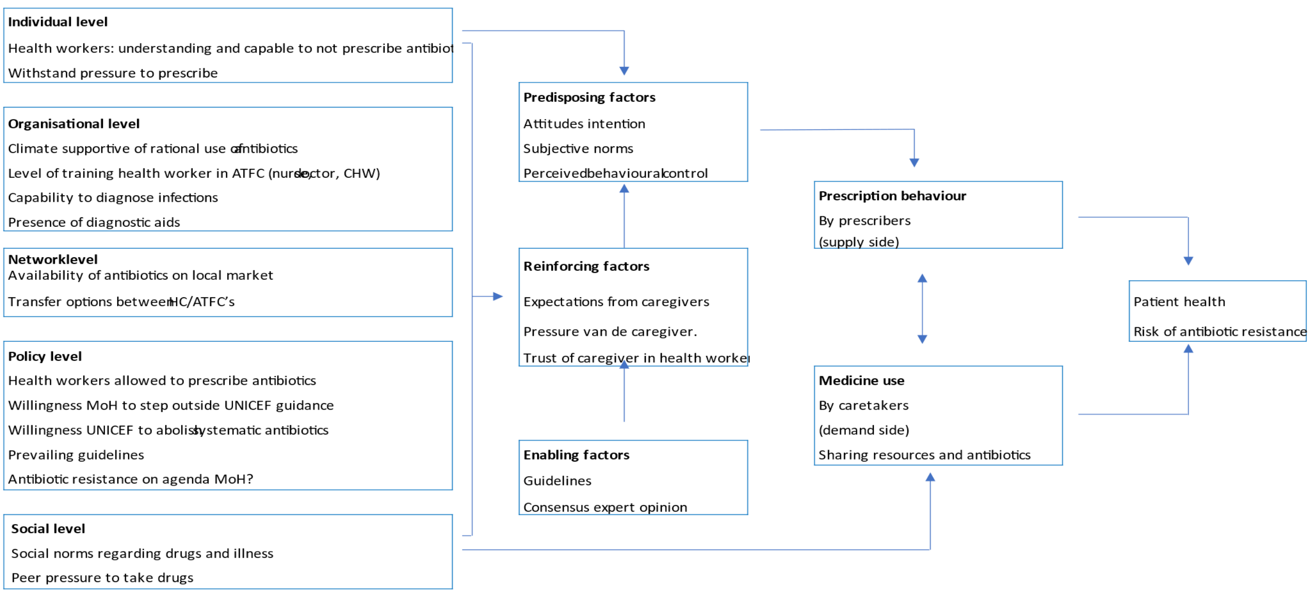


Figure 2: Adapted framework from Conceptual framework of the Antibiotic Smart Use model (22)

The framework describes different levels of influencing factors as interpreted for this study:

INDIVIDUAL LEVEL: the health care provider decides prescribing antibiotics or not. Factors that play a role include understanding or attitude and confidence of the healthcare worker in diagnosis and non-antibiotic treatment.

ORGANISATIONAL LEVEL: is the climate supportive of rational use of antibiotics, the level of training health workers in Ambulatory Therapeutic Feeding Centre (ATFC) (nurse, doctor or community health worker) their capability to diagnose infections and the presence of diagnostic tools (also rapid tests for malaria).

NETWORK LEVEL: referral possibilities to hospitals or inpatient therapeutic feeding centres (ITFC), availability of antibiotics in local market or possibility to sell drugs on a local market, distance to a health facility in case of development of complications (access) and possibility to coordinate approach to antibiotics between Health Centres (HC) or ATFC's.

POLICY LEVEL: level of health workers that are legally allowed to prescribe antibiotics. Willingness of WHO or UNICEF to abandon the systematic use of antibiotics. Possible financial repercussions for ministry of health (MoH) when willing to not follow guidelines. Presence of AMR on agenda of ministry of health

SOCIAL LEVEL: social norms in the community regarding drugs and illness that influences health worker actions.

There are PREDISPOSING, ENABLING and REINFORCING factors, that influence prescription behaviour of the health workers. Predisposing factors are attitude, subjective norms and perceived control of the healthcare worker. Reinforcing factors are expectations from caregivers (of the child), pressure of caregiver and trust of caregiver in health worker. Enabling factors are the existence and use of guidelines.

The OUTCOME is both patient health as well as public health, knowing that systematic antibiotics use without medical need leads to increased AMR and is as such public health risks. The patients' health is expressed in recovery rate from severe acute malnutrition . Recovery or cured is defined as: Weight for height> – 2 Z-score (or weight for height ≥85%) and absence of bilateral oedema and absence of acute medical issues for two consecutive weeks (23).

4. RESULTS:

4.1. OUTCOMES OF TRIALS AND RESEARCH ON SYSTEMATIC USE OF ANTIBIOTICS IN CHILDREN WITH UNCOMPLICATED SEVERE ACUTE MALNUTRITION IN SUB SAHARAN AFRICA.

A search in PubMed yielded 45 articles. After reading the abstracts, only 23 articles were eligible for closer inspection. After reading the entire articles, articles focussing on MAM, complicated SAM in high care situations, inventions with injectables or dietary protocols were excluded. Articles on a study protocol were also not included. A pilot trial was done in preparation for a large study in Burkina Faso comparing azithromycin to amoxicillin showing average weight gain 2.5 g/kg/day ([SD] 2.0) (azithromycin) and 2.6 [SD] 1.7) (amoxicillin group). The trial itself will be published next year only (24).

Four reviews (three including meta-analysis) and six single studies were identified on the use of systematic antibiotics in children from 6 to 59 months old with uncomplicated SAM in SSA.

REVIEWS:

Alcoba et al. (2013) conducted a systematic review and meta-analysis including three RCTs (one comparing amoxicillin to injectable, not included in this thesis for analysis), five Cochrane reviews, and 37 observational studies. Meta-analysis including 2767 uncomplicated SAM children favoured amoxicillin over cotrimoxazole: 42% (IQR 27–55%) vs. 22% (IQR 17–23%). They concluded that evidence for systematic antibiotics for uncomplicated cases was weak, and that placebo controlled RCTs were advised to gain further evidence on efficacy of antibiotics. This meta-analysis was conducted before the two RCT's on uncomplicated SAM in Sub Saharan Africa took place. The focus was much on the clinical aspects of SAM and antibiotics, and much less on the social determinants of health. Results were not analysed separately for HIV positive and HIV negative children. They did acknowledge the importance of having qualified staff to be able to identify infections in children (25).

Million (2016) published a meta-analysis on two studies in SSA: Trehan (26) and Isanaka (27). Recovery for the amoxicillin-group was better: RR 1.05, 95% [CI 1.00–1.11], p = 0.05, all forms combined: RR 1.03, 95% CI [1.00–1.06], p = 0.03). The results showed a small but significant difference between the two groups (28).

Williams & Berkley (2018), in their systematic review of the evidence for antimicrobial therapy (seven studies in SSA (including the studies described below), no pooled data) concluded that there is no justified reason to change the current protocol, and advised to continue with routine amoxicillin for ambulatory uncomplicated SAM patients (29).

Finally, Bitew et al. (2020) published a systematic review and meta-analysis on "treatment outcomes of severe acute malnutrition and predictors of recovery in under-five children treated within outpatient therapeutic programmes in Ethiopia". Nineteen articles were included, including three used for this thesis (see below) (30). They also included MAM studies and the ones that had a different study question, not focussed on antibiotics. They pooled estimates of hazard ratios and found that age > 24 months was not significantly associated with improved recovery rate (HR = 0.98, 95% CI: 0.81, 1.15, I2 = 80.8, P= 0.006) neither did deworming (HR = 1.04, 95% CI: 0.79, 1.28, I2 = 43.3, P= 0.133). However, children who presented with diarrhoea were 16% less likely to recover than children without diarrhoea (HR = 0.8, 95% CI: 0.75, 0.94). Absence of oedema presented a decreased recovery rate by 41% (HR = 0.41, 95% CI: 0.33, 0.50). Children who received amoxicillin had almost double chance of early recovery (HR = 1.81, 95% CI:1.18, 2.44) compared to children who did not receive amoxicillin. The review focused on clinical aspects and did not report on contextual or other factors that could have influenced the results. One reference was made in the discussion concerning the non-recovery rate. Factors mentioned here were not adhering to follow-ups, long distances to the health posts and sharing of food with family members. The reviewed study that reported about these factors did not specifically focus on antibiotics, but on multiple predictors of nutritional recovery (31).

SINGLE STUDIES (SEE TABLE 2):

1. Isanaka et al. (2016) conducted an RCT in Niger comparing systematic amoxicillin with placebo, and found no significant difference in recovery (Risk ratio (RR) 1.05, confidence interval (CI) 0.99 to 1.12, P=0.10). The amoxicillin-group had a reduced risk of 14% (RR 0.86, CI 0.76 to 0.98; P=0.02) to be transferred into an inpatient facility compared to group receiving placebo. There was some effect in terms of early weight gain in the group that used amoxicillin. There was no significant difference in nutritional recovery (primary outcome) (27).

2. Trehan et al. (2010) conducted a retrospective study in Malawi, which showed a lower recovery rate after four weeks for the children with amoxicillin (40%) versus 71% for children without antibiotics. However, after 12 weeks, the recovery rates were similar: 84% versus 86% (32).

3. Trehan et al. (2013) conducted an RCT in Malawi, comparing systematic amoxicillin, cefdinir and placebo. The study showed a lower proportion of recovery among children who received placebo compared to children who received cefdinir (5.8% lower, 95% CI, 2.8 to 8.7) and a suggested but non-significant lower recovery of the placebo group compared to the group that received amoxicillin (3.6% lower, CI 0.6 tot 6.7). Mortality was higher among the children in the placebo group than the group receiving amoxicillin (relative risk 1.55, CI 1.07 to 2.24) and cefdinir (RR 1.80; 95% CI, 1.22 to 2.64). In addition, the recovery rate of children receiving cefdinir was higher than in children receiving amoxicillin. One could argue that the difference could be related to less likelihood of resistance to cefdinir compared to amoxicillin (26).

4. Kabalo et al. (2017) did a retrospective cross-sectional study in Wolaita Zone in Ethiopia and found that children who received amoxicillin were recovering 1.52 times more likely than those not receiving antibiotics (Adjusted Odds Ratio (AOR) = 1.52, 95% CI (1.77, 3.89)). A high proportion of the children had oedema in this study (34.4%) these children had a higher recovery rate than children presenting with marasmus (AOR = 2.62 at 95% CI (1.77, 3.89). Default rates in this study were found to be low (2.2%) which could be due to the decentralised approach of the programme (33).

5. Shanka et al. (2015) conducted a retrospective longitudinal study in Kamba District, South West Ethiopia, which looked at determinant factors of success of OTP programmes. Children receiving amoxicillin had a better recovery rate than those without (AHR = 1.495, 95% CI 1.188-1.881). The type of health facility played a role: children treated at a health centre had 1.49 times higher probability to recover than children at a health post. (AHR = 1.50, 95% CI = 1.19, 1.89). Age also played a role: children over 2 years had a 1.25 times higher probability to recover than children aged less than two years (AHR = 1.255, 95% CI = 1.012, 1.556)

6. Abate et al. (2020) did a retrospective cohort study in Gubalafto Wereda, Ethiopia, and showed that children who received a course of amoxicillin showed 3.38 times higher recovery than the ones who did not (Adjusted Odds Ratio (AOR) = 3.38 at 95% CI (1.61–7.08)). The odds of recovery for children presenting with cough ([AOR = 0.47,95% CI: (0.28–0.80)] was lower than those without cough. The odds of recovery in children with diarrhoea ([AOR = 0.46, 95% CI: (0.25–0.86)] was lower than those without diarrhoea (35). Furthermore, the odds of recovery for children who were vaccinated were 6.85 times higher than non-vaccinated children (AOR = 6.85 at 95% CI (3.68–12.76)). It was 3.78 times more likely to recover for children who were newly admitted than those who were re-admitted (AOR = 3.78, 95% CI ((1.77–8.07))). This could be related to the fact that coughs and diarrhoea are often

associated with infections, that consume nutrients that otherwise could have been used for nutritional recovery. The difference in outcome in children who were fully vaccinated could be because immunization prepares the immune system, facilitating prevention of and fight against infections. Interestingly enough, amoxicillin is known not to work for diarrhoeal diseases (6).

Table 2: Summary of results

	First Author	**Research type**	**Country**	**OR or RR AB vs no AB**	**Conclusion**	**Quality GRADE**
1	Isanaka et al. 2016 (27)	RCT	Niger	RR 1.05, CI 0.99-1.12 P=0.10	No significant difference	Moderate
2	Trehan et al. 2010 (32)	Retrospective cohort study	Malawi	Recovery rate 4 weeks: 40% (+) vs 71% (-) 12 weeks: 84% (+) - 86% (-)	Worst with antibiotics after 4 weeks; No difference after 12 weeks	Low
3	Trehan et al. 2013 (26)	RCT	Malawi	Recovery rate Placebo vs amoxicillin 3.6% lower 95% CI 0.6-6.7	Better with antibiotics	Good
				Recovery rate placebo vs cefdinir 5.8% lower, 95% CI, 2.8- 8.7	Better with antibiotics	Good
4	Kabalo et al. 2017 (33)	Retrospective cross-sectional	Ethiopia	AOR = 1.52, 95% CI 1.09-2.11	Better with antibiotics	Moderate
5	Shanka et al. 2015 (34)	Retrospective longitudinal	Ethiopia	AHR = 1.495, 95% CI 1.188-1.881	Better with antibiotics	Moderate
6	Abate et al. 2020 (35)	Retrospective cohort	Ethiopia	AOR = 3.38, 95% CI 1.61–7.08	Better with antibiotics	Moderate

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework (36) was used to guide the assessment of the quality of the studies. It categorizes the quality of studies as good, moderate, low or very low. Grading starts with ranking the type of study: RCTs are in category good, while observational studies generally fall in the category low. After this, points are added or subtracted; points are added for not having confounders and direct evidence, or points are subtracted for limitations, inconsistency, uncertainty or bias. Appraisal of the quality of the studies in Annex III

Four of the six studies in SSA showed that the recovery rate of children who received antibiotics was significantly better than of children who did not. The study that found that children without antibiotics had worse initial outcomes was of low quality (32) and one study was performed in non-field conditions (27). Three of the reviews advise to continue with antibiotic treatment(28)(29)(37); one of them concluded that evidence was weak, but this was before any RCT was conducted(25) . The main outcomes of the studies were on clinical aspects. Meta-analysis showed small but significant difference in favour of systematic use of amoxicillin compared to no antibiotics. There was limited information on contextual factors, sometimes secondary outcomes were looked at, for instance lower recovery rates were mentioned in non-vaccinated children. A higher HIV prevalence, a high prevalence of oedema, lower levels of staff education, larger distances to a health facility, and food-sharing with family members were negatively influencing recovery rate

4.2. CONTEXTUAL INFORMATION TO THE OUTCOMES IN NIGER, MALAWI AND ETHIOPIA

INDIVIDUAL LEVEL

HEALTH WORKERS' ATTITUDE AND CONFIDENCE IN DIAGNOSIS AND NON-ANTIBIOTIC TREATMENT:

It was difficult to find relevant information about this. Only one article from Ethiopia was found. A survey from Belachew et al. (2022) among pharmacy-assistants who work in community drug retail outlets (pharmacies, street vendors, principle sources to access antibiotics for self-medication) in Ethiopia found that 77.9% of the staff had good levels of knowledge on antibiotic use and 76% had good knowledge on antimicrobial resistance (38). It is not sure if this information can be inferred on health care workers in primary health care centres (PHCs).

ORGANISATIONAL LEVEL

LEVEL OF EDUCATION OF HEALTH WORKERS:

The trial in Niger had a medical doctor present, which is not normally the case when children are treated in an ambulatory setting. (39). In Niger the programmes for Community- Based Management of Acute Malnutrition (CMAM) are largely dependent on NGO presence. (40). In Malawi and Ethiopia, many gaps in staff were reported .(41) (42). Mostly nurses and community health workers are in charge of the ambulatory feeding programmes. (43).

AVAILABILITY OF DIAGNOSTIC TOOLS:

Presence of rapid diagnostic tests (RDT) for malaria generally increases the confidence of health workers not to prescribe anti-malarials. However, it can lead to over- or under-prescription of antibiotics; if the test is negative, the cause of illness is not clear, an undertreatment or treatment with unnecessary drugs can be given. (44). In all three countries there are frequent problems with supply chain, which means that health centres find themselves without tests or drugs (45). This could lead to rupture of tests for malaria, resulting in overprescribing of antibiotics.

NETWORK LEVEL

REFERRAL POSSIBILITIES:

In Ethiopia, each health-post provides referrals to a health-centre (43). In the trial area in Niger, there was an MSF clinic in the vicinity. In Malawi, the Essential Health Package (EHP) is theoretically available to all, free at point of access; however there remain large variations in uptake of services. Not all people working at health centre level are aware of existence of EHP. (46). Bossyns et al (2005) found that in Niger in rural areas: referrals are too few and come too late (47). Kaunda et al (2021) found in Malawi that barriers to referral were distance and unavailability of transportation (48).

ANTIBIOTICS IN LOCAL MARKET:

Evidence shows that antibiotics are widely available and bought without prescription in all three countries; counterfeit drugs and antibiotics can be found in all three contexts. (49) (50) Inappropriate use of antibiotics such as wrong indication for antibiotics, wrong dose, discontinuation by patients when symptoms subside happen on all levels, primary, secondary and tertiary. Gebeyehu et al (2015) found no significant difference between urban and rural communities in inappropriate use of antibiotics in Ethiopia (51).

DISTANCE TO A HEALTH FACILITY:

In Niger, 58.5% of the population lives further than one hour walk from a health post (52). People in remote villages have additional costs for transport to the HP and for buying medication if medication is not available in the HP (53).

A prospective cohort study in Ethiopia mentioned that long distance to a health post is a risk factor of non-recovery of nutrition treatment (31). Also found Kabalo et al. in Wolaita Zone Ethiopia: living within 25 minutes walking distance of a health facility was associated with a 1.53 times higher odds to recover than living further away (AOR 1.53, CI 1..1 to 2.12) (33).

In contrast to the findings of Kabalo et al: Trehan et al. (2013) found that in Malawi the distance to a health centre did not influence the recovery rate (26).

POLICY LEVEL

AMR ON AGENDA MINISTRY OF HEALTH (MOH):

There is no clear programme nor a committee concerning AMR in Niger, in contrast to the other two countries. In Malawi, the MoH has an Antimicrobial Resistance Strategy 2017 – 2022 (8) and Ethiopia developed and approved a 'National AMR Surveillance Plan' for laboratory-based AMR surveillance in 2017 (54). In 2019, the Ethiopian Food and Drugs Administration clearly stated that a dispenser is not allowed to dispense 'prescription-only-medication' without prescription (55).

HEALTH WORKERS ALLOWED TO PRESCRIBE ANTIBIOTICS:

In all three countries treatment for malnutrition is part of the essential health package. The Integrated Management of Childhood Illness (IMCI) includes prescription of antibiotics (45) (43) (53). This means in all three countries the health care worker is allowed by the MoH to prescribe antibiotics for malnourished children.

SOCIAL LEVEL

NORMS REGARDING DRUGS AND ILLNESS:

Community-based survey among adults in Ethiopia showed that 48.5% took antibiotics in the past year, of which 35.9% of them used them inappropriately: bought in the market without prescription and discontinued use when symptoms subsided. Amoxicillin (72%) was the most commonly used antibiotic (56). Similar studies with similar results were done in Malawi by Sambakunsi et. al. (2019) (57) and in Niger by Jifar et. al.

(2018) (53). In markets the drugs are often counterfeit (fake) (58). These drugs may contain lower levels of antibiotics and are known risk factors for AMR, especially if not enough or fake drugs are being used.

PREDISPOSING FACTORS

ATTITUDES, INTENTION, NORMS, PERCEIVED CONTROL OF HEALTH CARE WORKER:

For none of the context's, information on this was found.

REINFORCING FACTORS

PRESSURE / EXPECTATIONS FROM CAREGIVERS:

No information was found on Niger. In Malawi, 92.4% of the respondents in a survey believed that antimicrobials are used to stop a fever and expect to get antibiotics prescribed when they are not feeling well (57). A cross-sectional study from Gondar (Ethiopia) showed that 83% of the people thought that antibiotics speed up recovery from illnesses that do not require antibiotics (59). This suggests that people will try to obtain antibiotics from the health worker.

ENABLING FACTORS

GUIDELINES:

In all three countries WHO guidelines are available. In Ethiopia, national guidelines are also available in local languages. In Malawi 2016 CMAM guidelines are available (60). In Niger Libbey (2000) reported that in Niger treatment guidelines were available in all but one facilities (61).

DEMAND SIDE

MEDICINE USE:

In Niger, Bedford et al. (2014) found that parents found it difficult to remember instructions they were given on how to administer antibiotics to their children. They often stopped treatment prematurely. Antibiotics were cheaper on markets than in health facilities, so were often bought there (53). Similar findings are found in Malawi: self-medication is common practice. People obtain antibiotics from market vendors, pharmacies, or use left-overs from previous treatment, and drugs are being shared. Factors that influence self-medication are lack of medical supplies, travel distance to a health facility, poor attitudes of health workers and past negative experiences (57). In Gondar (Ethiopia), they did a study on people taking medicine: 67.9% did not finish their course of antibiotics when they felt better (56). These are all known risk factors for AMR.

Teshome et al (2019) found in their study in Ethiopia, that one predictor of child recovery was maternal literacy. They related this to better feeding and caring practices and better economic status (31).

SUPPLY SIDE

PRESCRIPTION BEHAVIOUR:

A study in Malawi concluded that health workers' compliance with general prescription standards was only about 50% (61).

In Ethiopia, two conflicting study results were found. One study on general prescription behaviour concluded that prescribing and dispensing practices in government health centres are fairly good and are not that far from the standard WHO requirements (62). Another study that was conducted two years later in comparable setting: outpatient departments of governmental hospitals in the same area of Eastern Ethiopia concluded the opposite: “Overall, none of the core prescribing indicators was in line with the WHO standards” (63).

4.3. FACTORS THAT INFLUENCE ANTIMICROBIAL RESISTANCE (+/-) IN SUBSAHARAN AFRICA

The WHO identified most important drivers of AMR (64):

1. “Overuse and misuse of antimicrobials, both in humans and animals.
2. Lack of access to clean water, sanitation and hygiene (WASH) for humans and animals
3. Poor infection and prevention and control (IPC) in health-care facilities and on farms
4. Poor access to good quality and affordable medicines, diagnostics and vaccines.
5. Lack of knowledge and awareness.
6. lack of enforcement of legislation.”

4.3.1. OVERUSE AND MISUSE OF ANTIMICROBIALS, BOTH IN HUMANS AND ANIMALS

Any use of antimicrobials, even if appropriately used and justified, can contribute to development of resistance. This developing resistance is aggravated by excessive and unneeded use of antibiotics (65). In low- and middle-income countries, self-medication is common practice and patients often get antimicrobials without prescription. The supply chains are not regulated, resulting in lower contents and even ineffective drugs, not properly stored and over-heated drugs. Some patients seek treatment from traditional healers, these provide them with herbal products for the treatment of infections. These substances could potentially increase pathogen strength and thus contribute to the development of resistance (65).

Inappropriate use of antibiotics amplifies AMR which is related to poverty. But also rich people stop taking the drugs when they feel better. This can lead to patients having a more resistant and potentially more virulent strain of the pathogen. By not continuing the treatment, surviving bacteria are exposed to sub-therapeutic levels of antimicrobials and increase the risk of developing resistance (66).

Vink et al. (2019) state “Between birth and age 5 years, children in LMICs are prescribed a remarkably high number of antibiotics. A large proportion of these prescriptions appear to be unnecessary. National and local efforts to reduce unnecessary prescription of antibiotics to children would likely improve both patient wellbeing (in terms of preventing side-effects) and reduce the global threat of antimicrobial resistance”(67).

4.3.2. LACK OF ACCESS TO CLEAN WATER, SANITATION AND HYGIENE (WASH) FOR HUMANS AS WELL AS ANIMALS

AMR is a big issue in Ethiopia. A meta-analysis found that the pooled prevalence of 20% AMR bacteria were found in food producing live animals. In milk, AMR were detected, of these 69% were resistant to penicillin and 51% for amoxicillin (68). Abera et al. (2016) demonstrated presence of ESBL-producing bacteria not only in clinical sources, but also in drinking water samples (57.6% and 9.4%) respectively (69).

Kurowskiet al. (2021) conducted a longitudinal study including stool-samples and survey questions on WaSH, socioeconomic status, householdsize and proximity of animals in Peru (70). Children living with over 11 animals had increased odds of colonisation with resistant Escherichia coli (OR: 5 1.94, 95% CI: 1.05–3.60). When they could smell poultry, the odds to have AMR positive samples were also increased (OR 5 1.72, 95% CI: 1.11–2.66), suggesting a role for animals or poultry in the risk of carrying AMR bacteria in children. This set-up of studies was not found in Africa, however many studies show a cross-over of AMR to human in Sub Saharan Africa (71) (72). These studies show high levels of AMR carriage in poultry, transmission, but do not specify presence in children. Eyasu et al (2017) saw bacterial isolates were multi-drug resistant, especially for ampicillin (94%) and penicillin (92%). Both these antibiotics are comparable to amoxicillin (73).

4.3.3. POOR INFECTION AND PREVENTION AND CONTROL (IPC) IN HEALTH-CARE FACILITIES AND ON FARMS

Maataoui et al. (2020), in a study embedded in the trial in Niger, looked at ESBL-E carriership in SAM children and their siblings under 5 years. At start, the prevalence was the same in both groups, but acquisition of ESBL-E in the children with amoxicillin group was significantly higher (53.7% versus 32.2%, adjusted RR = 2.29, *P* = 0.001) than in the placebo group. Also from the siblings of the children in the amoxicillin group 11.5% had a similar ESBL strain (indication of ESBL-E transmission), compared 3.8% (4/105), *P* = 0.04] from the placebo group (74). Both p values are below 0.05, making them significant, even if the numbers of included children was not very large.

Woerther et al. (2011) conducted a prospective study in Niger. Admitted children in a nutrition ward were enrolled and checked for acquisition of ESBL-E in the hospital. At admission, 31% of the children carried ESBL bacteria. The non-carriers were retested at discharge; they had an acquisition rate of 94%. This suggests that people can easily get colonized with the ESBL-E bacteria, with the risk of spreading this in the community. Their conclusion is to make a careful risk versus benefits analysis for antibiotics. In addition, more strict hygiene measures are needed (75).

Lester et al. (2020) published: “Estimating the burden of antimicrobial resistance in Malawi”. They examined bloodculture data from patients from Queen Elizabeth Hospital, show a quick rise in resistance against commonly used drugs like ceftriaxone (increased AMR) (76).

4.3.4. POOR ACCESS TO GOOD QUALITY AND AFFORDABLE MEDICINES, DIAGNOSTICS AND VACCINES

In Niger, officially, care and medication are free of charge for children under five. However, there is a lack of free medicine at the health posts and stock outs happen very frequently, so people have to buy their antibiotics (53). Erku et al (2017) studied use of antibiotics in the general population. As people buy antibiotics in markets, the quality of the drugs is questionable (56).

Research on health seeking behaviour by Bedford et al. (2014) showed that health posts in Niger were understaffed. They offered limited services and opening hours were limited, restricting access in particular at night (53).

4.3.5. LACK OF KNOWLEDGE AND AWARENESS

Studies show, that in the study areas there was a lack of knowledge or adherence to protocols, Ethiopian studies gave conflicting results (62)(63).

4.3.6. LACK OF ENFORCEMENT AND LEGISLATION

Two of the study countries had a policy on AMR. Only one of them had a formal legislation; in all three countries they are far from implementing law enforcement on drugs selling on the markets nor strategies to reduce counterfeit drugs or regulate the rules for prescription of drugs.

4.4 FACTORS AND SITUATIONS IN WHICH PRESCRIPTION IS MORE BENEFICIAL, BALANCING AMR AND INDIVIDUAL RISKS AND MAKE RECOMMENDATIONS ACCORDINGLY.

Originally, we planned for eight experts to be consulted. In the available timeframe seven experts were consulted for this study.

The research in Niger (Isanaka 2016) states no difference in outcome was found in the groups with and without amoxycillin. However, four experts stated that the study in Niger did show a difference in outcome, namely in the referral rate of the children. There were more referrals in the group without antibiotics.

CURRENT PRACTICE TO SYSTEMATICALLY GIVE ANTIBIOTICS TO ALL CHILDREN WITH UNCOMPLICATED SAM

All but one expert said the systematic use of antibiotics for children with uncomplicated SAM is a good practice, based on current evidence. "Would love to stop giving them, but so far the data proves we need them." Only one expert stated that it *used* to be a good practice when introduced prior to our understanding of AMR. While all experts agreed that many children do probably not need antibiotics, there is currently no way on how to detect and decide who does not need them. A quote: "Many children with SAM do not need antibiotics, the question is to find which ones do and which ones don't; that's the real question now."

A majority (5/7) of the experts was against a tailor-made decision for each child. They thought that a standard protocol should be used instead of a personal decision. Reasons were inadequate levels of staff training (capacity to examine a child properly), avoidance of confusion, sustainability and lack of capacity of the MoH. Incomplete vaccination status was an argument to five people. One expert added that the pressure from community to prescribe antibiotics is often huge.

The focus of the interviews was on systematic antibiotics, but experts admit that there is little certainty whether the drugs are properly used. A quote "We have a tendency to lean to antibiotics, but we do not even know how these drugs are being taken. Antibiotics are shared, people don't complete courses, and they openly talk about it. This part is very difficult to quantify so we shut our eyes to it."

Most mentioned issue was decentralisation of treatment of malnourished children in the community by low-trained staff. Withholding systematic antibiotics while working with low-trained health workers would result in an increased risk of not treating with antibiotics while this is needed. All respondents believed it is less harmful to treat some children with antibiotics who do not need it, than to not give it to the ones who do need it.

REASONS NOT TO GIVE ANTIBIOTICS

When asked about reasons for stopping the systematic use of antibiotics for children with uncomplicated SAM, five of the seven experts would not consider this. If research would be aimed at investigating which factors would enable a decision to stop systematic use, it should focus on vaccination status (mentioned by five respondents), as well as level of the healthcare worker (the higher the level of education, the better).

Factors considered to stop giving routine antibiotics were: Properly trained staff, easy access, frequent follow-ups, no stock-outs, knowledge on background AMR and mortality. Added was if amoxicillin is no longer useful, that might be another reason to omit or change. However, “If you change to another antibiotic, you might increase the risk of AMR even more”.

Despite the experts mostly agreeing on continuation of systematic antibiotics, one paediatrics referent had an example in which there could be a deviation possible from protocol: There is a programme in which Action Contre la Faim (ACF) is doing a programme with integrated nutrition in which community health workers are treating SAM children, outside of an ambulatory feeding setting, in the community. This is a good strategy to increase coverage for malnutrition. In some countries these health workers are not allowed to prescribe antibiotics. If then the choice is treat without antibiotics versus not to treat at all, it would be justified to treat without. You will treat more children sooner, so will save more lives

BACKGROUND MORBIDITY INFLUENCE

There was no consensus at all among the seven respondents. For example, one person stated that no matter what, children with SAM do require antibiotics. One expert said it depends on the disease: all children with respiratory tract infections, high or low should receive antibiotics. Another expert stated that in case of viral disease it is of importance not to prescribe antibiotics. All experts agreed that in case of a measles outbreak, all children with uncomplicated SAM need to get antibiotics.

HIV prevalence: all agree that this group of children belong in an HIV treatment programme, and should get antibiotics. If children are already diagnosed, they already receive antibiotics as part of their treatment. Three experts would add amoxicillin; the other ones would not.

CONTEXTUAL FACTORS

Four respondents mentioned that the background of AMR in a region is of vital importance, if one would consider to change a protocol, while they also acknowledged that this information is most often lacking, acknowledging that the risk of giving antibiotics which do not work is substantial.

Conflict, displacement and crowding are factors that increase the risk of infection and therefore increase the already existing need for antibiotics.

Factors that influence outcome for children positively: Access to healthcare, both outpatient and inpatient care, the level of education of healthcare workers, the level of education of caregivers.

Influencing factors which could positively or negatively influence outcome are: gut colonisation, dietary differences, environmental bacteria, bacteria in food, exposure to other antibiotics and caregivers do or do not properly administer antibiotics they have been given.

The experts were asked if they would see different recommendations for different context, or if there were conditions in which they would consider to deviate from current protocol:

One of the experts stated that not one factor is the silver bullet and that there should be flexibility in different contexts when possible. Favourable conditions should give reason to adjust the current recommendations.

As an AMR expert gently put it: “It is easy to start doing systematic antibiotics, but very difficult to stop to do something. Suddenly it would seem you prioritise AMR over malnutrition, which will be a difficult battle to fight. Doctors have individual contracts with their patient, they do not have a contract with global health. This is why this is a difficult battle to fight AMR.”

5. DISCUSSION

Extensive research has shown that the prescription of antibiotics that are not strictly needed is a risk for the development of antimicrobial resistance. The focus of this thesis was on routine use of amoxicillin in uncomplicated SAM children. In light of the threat of growing antimicrobial resistance, the humanitarian community currently raises the question whether to give all children with uncomplicated SAM antibiotics, despite this being a WHO recommendation. A review of the evidence, including contextual factors that influence outcomes for patients and public health, as well as expert opinion could offer new insights.

SYSTEMATIC ANTIBIOTICS USE AND PATIENT OUTCOMES

From the six studies in SSA that studied patient outcomes with or without routine use of amoxicillin, four studies showed significant improvement in recovery rate with antibiotics. At first sight, two studies showed no significant difference in recovery rate with or without antibiotics, but the low quality of one study (Malawi) (32) and the excellent conditions with high quality staff and early referral, which are not comparable with a non-study setting, in another study (Niger) (27) decrease the validity of the study findings.

Although the recovery rate was not significantly different between the two groups in Niger, the risk of deterioration and transfer into an inpatient facility was significantly higher in the group that did not receive amoxicillin versus the group that did receive amoxicillin. This could have been due to poor clinical status of the children without antibiotics, but it could also be linked to lower threshold for referral during the trial. Quite some children in the control group were referred to the hospital; this could have masked potential adverse outcomes such as mortality or default. No explanation was presented in the study.

The drawback of systematic antibiotics is the rise of AMR, not only in the individual patient (when not properly taken) but also in others as it spreads in the community, making antibiotic less effective to treat infections.

Based on patient outcomes, the use of systematic amoxycillin is preferable over non-use of amoxicillin for SAM children in ambulatory settings.

CONTEXTUAL FACTORS

The three countries where the research on the routine use of amoxicillin took place are all low- and middle-income countries in the Sub-Saharan region. However, there are differences in the contexts between these countries. In terms of disease patterns and burden, in Malawi the prevalence of HIV among the population is significantly higher than in the other two countries. This could have had an influence on the outcomes of the studies which were held there. It is known that HIV alters the immune system and children with HIV are more prone to infections. In the framework used in this thesis, HIV prevalence is not mentioned, while this could be a serious consideration in the choice whether or not to give antibiotics.

Travel distance to a health facility can hinder caregivers in seeking treatment in time, or to be able to come for follow-up visits, or come back early when complications occur. This could be an argument in favor of giving antibiotics. One can also argue that longer distance to a health facility can be linked to a rural environment and therefore to a generally lower educational level of the mothers, which is a demonstrated risk factor for no or delayed cure of SAM. Interestingly enough, in one study the travel distance did not make a difference in outcome whereas in others it did; an explanation for this has not been found.

Educational level can be related to administering antibiotics in a correct way. Rural setting can be linked to poverty and being less able to purchase food commodities as well as having less proper hygienic possibilities. This could in turn lead to more diarrhoeal episodes as well as increased risk for the children to be malnourished.

Food shortage alone is rarely a problem, most often it is accompanied by conflict, displacement, or general decline of a health system and services. Often hygienic conditions deteriorate, which increases infection pressure and puts vulnerable children more at risk to get an infection. Even if an infection is viral by origin, the circumstances and lowered immunity of these vulnerable children would not allow for a 'wait and watch' approach.

It is clear that current research focused on patient outcomes favors the systematic use of antibiotics. In addition, circumstances that make most experts want to continue systematic antibiotics are lower levels of education, not only of the healthcare workers, but also of the caregivers, and travel distance to the health facilities. In these circumstances, providing an antibiotic safety net is considered even more important. In case of an outbreak of measles, all experts agree that antibiotics are mandatory.

RISK ON AMR IN THE COUNTRIES

There is limited data on carriership of antimicrobial resistant bacteria in the three countries. It is not apparent that the presence of an AMR steering committee has any influence on the prevalence of AMR. Capacities to test are not available or very limited on a local level. In areas where there is a high prevalence of SAM, data on AMR are most often lacking; these data could be used to tailor the protocol in local settings taking into account the local resistance patterns.

Most countries in Sub Saharan Africa do not have good strategies for surveillance of antimicrobial resistance. They lack laboratories to test and lack quality assurance and these labs. In addition, programs for infection prevention and control (IPC) are not well established. Hence it is difficult to gather substantial evidence in the three countries on real levels of AMR. In all three countries, antibiotics can be bought in the local market without prescription and in all three countries, the availability of good quality drugs is not always guaranteed, all these factors increase the risk of AMR. This practice is wide-spread and very difficult to control, influence or change.

The culture of sharing antibiotics as well as food and other commodities may play a role in the development of AMR, but it is very difficult to examine this, let alone influence this behavior; it may take years before a change could be observed.

AMR is a multifactorial public health problem, which requires combatting on all levels, not only in the medical field, but also on governmental and international level. The contribution of routine use of amoxicillin in uncomplicated SAM children to AMR is not determined.

RISKS AND BENEFITS OF SYSTEMATIC ANTIBIOTICS:

Two studies in Niger showed infection with AMR in the hospital not only in the admitted children, but also in their siblings. However, no studies were found to compare these data on an outpatient level; it seems very likely that children are more at risk to acquire resistant strains in hospitals, due to lack of hygiene, overcrowding and nosocomial infections.

One could argue that if children are prevented from being admitted, this would decrease the risk of acquiring AMR and thus slow down the spread of AMR. In this case, an argument could be made in favor of systematic antibiotics in ambulatory settings; this could potentially decrease the risk of need for hospital admission and therefore prevent AMR. The question remaining would be how many children would be prevented from admission in an inpatient facility, when receiving antibiotics versus no antibiotics, and how this compares to possible acquisition of AMR among children in ambulatory settings as a result of wrong use of antibiotics.

Most expert are reluctant to give way for a non-systematic approach. The systematic approach avoids having different ways of working between different places, resulting in possible inequity, or even tensions between populations if people feel they are treated differently. Health workers with high levels of education and skills are often not available. In that case, a 'safety net' of systematic use of antibiotics is the safest way for the individual child. Other influencing factors are high vaccination coverage, shorter distance to a health facility as well as having food shortages only, without complicating factors. These arguments, however, do not outweigh the risk for deterioration of the child and are not enough reason to give up current protocol.

No studies have been published yet, that giving antibiotics in uncomplicated SAM children increases AMR on a population level. It could be argued that even if antibiotic prescription might lead to an increase in AMR, individual healthcare workers do not see this as an argument to withhold antibiotics, especially when facing SAM children, about the most vulnerable group of patients one can have.

Benefits of not doing systematic antibiotics are on global level, not in the individual level. For a health care worker the patient in front of him or her is the most important; AMR is an abstract thing, that is related to public and global health. They have a contract and obligation to a patient, not to an emerging, abstract global health problem.

ANALYTICAL FRAMEWORK

For this thesis, I chose to use an adapted framework with the healthcare worker as a central point. The strength of the framework is that it looks at other factors besides the patient. The weakness of this framework is that the clinical condition of the individual patient (in front of the healthcare worker) does not really appear in the framework. Similarly, the HIV prevalence could be a serious consideration in the choice whether or not to give antibiotics.

Information on some of the social factors were not found in the literature; especially on the individual level of the health worker. Literature on the predisposing and reinforcing factors was very limited. Prescribing of antibiotics in SAM children should be looked at in a holistic way, taking into account the different levels and the individual as well as the public health outcomes. This study has shown that all factors play a role and should be studied as well.

An important finding is that the level of education of the health worker plays a role in the number of transfers towards an inpatient facility. In addition, the level of education of the health care worker is important to be able to diagnose certain underlying conditions. The level of education of health workers could have been reported upon in individual level, but in the original framework, this part is reserved for the attitude and confidence of the health worker.

For future use of the framework, it would be useful to add a more robust section on patient characteristics and the local antimicrobial resistance patterns in the areas of study.

LIMITATIONS OF THE STUDY

Little information was available on social determinants or contexts within the studies. A wider search revealed some relevant information on the contexts, but information on outcomes of systematic use of antibiotics in SAM children in ambulatory settings on AMR is lacking. It is therefore very difficult to draw solid conclusions.

Another limitation was the time frame, in which the end of the academic year and the deadline of the study coincide with the summer-holiday season.

The strength of this study is that I have taken a different approach, using mixed methods and using a comprehensive framework including the perspective of the prescriber, and taking the social context into account.

6. CONCLUSION

Based on the current context in sub–Saharan Africa and the current evidence, systematic antibiotics are needed for SAM children in ambulatory settings, despite potential risk on increased AMR.

Not giving systematic antibiotics to children with uncomplicated SAM may increase the risk of hospital admission, resulting in an increased risk of AMR as well, on top of an increased risk of a poor outcome of the child's health.

7. RECOMMENDATIONS

For practitioners: Should continue systematic antibiotics in all children with uncomplicated SAM.

For researchers: More studies are needed which should include contextual factors, as well as AMR patterns.

A focus of study could be to identify predicting factors for children who are at risk of deterioration, which could lead to a more tailored approach.

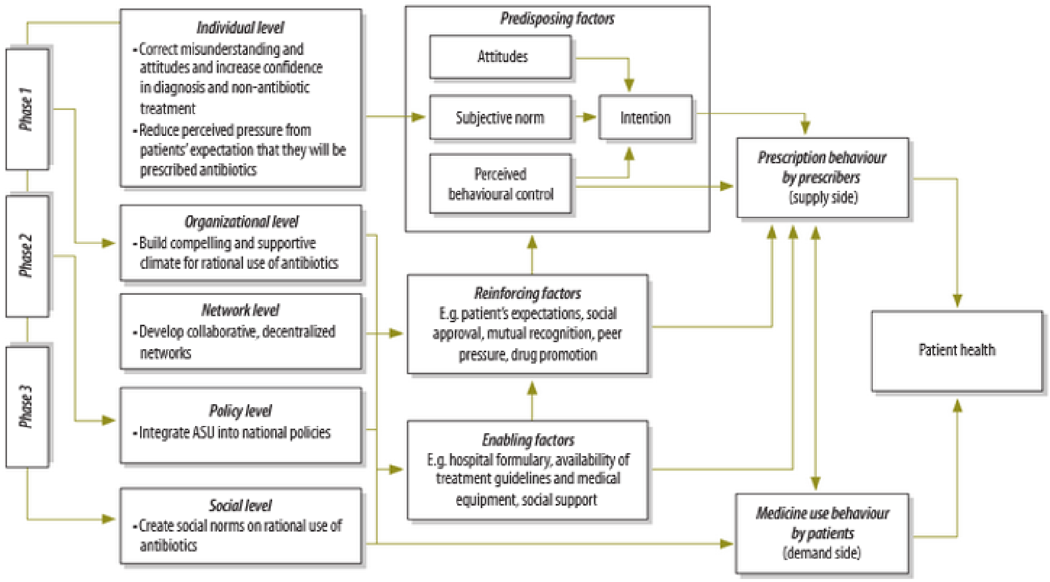
For governments: There is a need to improve surveillance on AMR, not only in hospitals, but also in ambulatory settings.

8. ANNEXES

ANNEX I: SEARCH TERMS USED

Top part for studies on systematic antibiotics in uncomplicated SAM children. Bottom part to find additional information. Variations have been used for the different sub-objectives and in addition snowballing technique has been used.

	"Children 6 to 59 months" AND "Uncomplicated SAM" OR "Acute malnutrition" OR "Severe Acute malnutrition" OR "malnutrition" OR "Undernourishment" OR "Acute undernutrition" OR "Kwashiorkor" OR "Marasmus" OR "Wasting" OR "Weight for Height" OR "MUAC" OR "Mid upper arm circumference" OR "Nutritional oedema" OR "Bilateral pitting oedema" OR "Therapeutic food" OR "Ready-to-use therapeutic foods" OR " RUTF " OR Plumpynut OR "Management of acute malnutrition in children" OR ATFC OR CMAM OR OTP.
AND	
	Amoxicillin OR Cefdinir OR Routine antibiotics OR Systematic antibiotics OR antimicrobials OR antibiotics
AND	
Geographical terms:	Sub Saharan Africa OR Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroon OR Cape Verde OR Central African Republic OR Chad OR Comoros OR Congo (Brazzaville) OR Congo (Democratic Republic) OR Côte d'Ivoire OR Djibouti OR Equatorial Guinea OR Eritrea OR Ethiopia OR Gabon OR The Gambia OR Ghana OR Guinea OR Guinea-Bissau OR Kenya OR Lesotho OR Liberia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Réunion OR Rwanda OR Sao Tome and Principe OR Senegal OR Seychelles OR Sierra Leone OR Somalia OR South Africa OR Sudan OR Swaziland OR Tanzania OR Togo OR Uganda OR Western Sahara OR Zambia OR Zimbabwe
factors	"Individual level" OR "Health workers" OR "prescribe antibiotics" OR prescription OR "Organisational level" OR "supportive of rational use of antibiotics" OR "level of training health worker" OR nurse OR doctor OR "community health worker" OR "diagnose infections" OR "diagnostic test" OR "rapid test malaria" OR "paracheck" OR bioline OR "Network level" OR "Health center" OR hospital OR "referral" OR "Ministry of Health" OR UNICEF OR guidelines OR AMR OR "antibiotic resistance" OR "Social level" OR "social norms" OR "Peer pressure" OR "Predisposing factors" OR attitudes OR norms OR behaviour OR control OR "Reinforcing factors" OR expectations OR pressure OR Trust OR "Enabling factors" OR guidelines OR consensus OR "expert opinion" OR disease OR health
AND	
factors	Cefdinir OR Amoxicillin OR Routine antibiotics OR Systematic antibiotics OR antimicrobials OR antibiotics) AND ("indicators of antimicrobial resistance" OR AMR OR "Antibiotic resistance" OR "Antimicrobial stewardship" OR "Extended-spectrum β-lactamase producing enterobacteriae" OR "antimicrobial resistance" OR "Over-prescription of antibiotics' OR "entire antibiotic course" OR "Overuse of antibiotics" OR antibiotics in livestock "infection control" OR IPC OR " hygiene and sanitation" OR WASH



Antibiotic Smart Use model, a model to promote the rational use of medicines, starting with antibiotics (22)

ANNEX III: APPRAISAL OF QUALITY OF STUDIES:

The GRADE framework (36) was used to guide the assessment of the quality of the studies. The quality of the studies was divided in good, moderate, low and very low quality.

1. Isanaka et al. (2016): RCT Niger (27)

GRADE: Moderate. Potential bias and possibly difficult to extend the findings. The level of training of staff for follow up is of importance. In the study setting, there was extensive trained staff present, who have skills to detect possible development of complications, and there was a referral option nearby. These conditions can probably not be fully met in other settings, where staff is less trained and travel distances are longer. Another remark is that children presenting with oedema were not included in the study, whereas in the case definition of SAM they should have been included. This could potentially be a selection bias.

Overall, the percentage of children transferred into an inpatient facility was extraordinarily high in this study: 26.4% in the amoxicillin group vs. 30.7% in the placebo group. Transfer rates in the other studies were much lower: Kabalo 5.1%, Shanka 1.6% and Abate 17%. Last point was that the p-value was taken as 0.10, instead of the scientific norm of 0.05. However, changing this would not influence the conclusion of no difference between the study arms.

2. Trehan et al. (2010): Retrospective study Malawi (32)

GRADE: Low. The cohorts were from two different districts, which could lead to bias. Data were collected retrospectively, which increases the risk of a selection bias or a possible confounding factor. Baseline characteristics in the two groups were slightly different, which is mentioned in the analysis. This study was followed up with RCT.

Retrospective of the publication, the quality of the study was further questioned by the authors themselves, as the cohorts differed greatly: not the same teams provided care, it compared the work of two different organisations, and two different contexts: southern Malawi and central Malawi. There were also different levels of training of staff. The amoxicillin group did not use the drugs consistently, as they had food stock-outs. The outcomes were, in hindsight and according to the authors, more related to circumstances and the teams implementing the malnutrition care.

3. Trehan et al. (2013): RCT Malawi (26)

GRADE: Good. Appropriate randomisation, appropriate double blinding, appropriate follow-up and sample size. Remarks: Malawi has a high prevalence of HIV, plus a relatively large percentage of kwashiorkor in the study. The study did not stratify for HIV, this is a potential for bias as treatment of HIV could modify the effect of amoxicillin and cefdinir (77).

4. Kabaloet al. (2017): Retrospective cross-sectional study Ethiopia (33)

GRADE: Moderate. Sufficient numbers of patients included. High number of oedema, possibly selection bias. The study found that there were gaps in reporting recovery.

5. Shanka et al. (2015): Retrospective longitudinal study Ethiopia (34)

GRADE: Moderate. Sufficient numbers of patients included; potential inconsistency as 33% of the children stayed >8weeks in the programme.

6. Abate et al. (2020): Retrospective cohort study Ethiopia (35)

GRADE: Moderate. Sufficient numbers of patients included. Potential selection bias was that children under two years were 70% of the studied population.

7. Alcoba et al. (2013)

GRADE: Good. Meta analysis on observational data

8. Million (2016)

GRADE: Good. Meta analysis on big sample size

9. Williams & Berkley (2018)

GRADE: Good. Systematic review

10. Bitew et al. 2020

GRADE: Good. Systematic review and meta analysis

Informed consent form

Informed Consent Form for experts on malnutrition and / or antimicrobial resistance, who we are inviting to participate in research titled: How smart is the use of systematic antibiotics in the treatment of uncomplicated SAM? Subtitle: What are the individual and public health risks and benefits of the routine use of amoxicillin in the treatment of Severe Acute Malnutrition in ambulatory settings in Sub Saharan Africa?

Name of Principle Investigator: Erna Rijnierse

Supervisor: Saskia van der Kam (MSF OCA nutritional advisor)

Maryse Kok (KIT academic advisor)

This Informed Consent Form has two parts:

- **Information Sheet (to share information about the study with you)**
- **Certificate of Consent (for signatures if you choose to participate)**

You will be given a copy of the full Informed Consent Form

Part I: Information Sheet

Introduction

My name is Erna Rijnierse, I am a Dutch Medical Doctor, and have worked for a long time in the humanitarian field as emergency team member for Médecins sans Frontières (MSF). At the moment am doing a thesis for my masters in international health at the Royal Tropical Institute (KIT) in Amsterdam. The area of interest is the systematic use of antibiotics in uncomplicated malnourished children between the age of six to 59 months in Sub Saharan Africa. I would like to make a risk versus benefit analysis of the routine use of amoxicillin in the light of the emerging antimicrobial resistance. Studies that compared systematic antibiotics with no systemic antibiotics in the treatment of uncomplicated malnutrition are analysed on both patient outcome (in terms of recovery rate or odds ratio of recovery) and public health outcome, specifically an increased risk of developing antimicrobial resistance. I have also looked at different aspects: individual prescriber, organizational, the network, policy and social aspects. I would like to present you the outcomes of the literature review and then learn from your experience and knowledge on the topic. I would very much appreciate your participation in an interview or panel discussion on this topic.

Purpose of the research

The objective of the research is to identify contextual factors that might influence the individual and public health risks and benefits of the routine use of amoxicillin in the treatment of Severe Acute Malnutrition of under-5 children in ambulatory settings in Sub Saharan Africa. To this end a literature research has been conducted and your expert opinion will provide more extensive insight in the matter. The ultimate goal is to come up with recommendations in what situations or settings the systematic use of antibiotics is more beneficial and in what circumstances it may be more of a risk than a benefit.

Type of Research Intervention

For this research, we have done a literature review, which we would like to complement with your contribution to a discussion or by interview.

Participant Selection

You are being invited to take part in this research because we feel that your experience and knowledge as an expert can contribute much to our understanding of the topic, and in combination with other experts, may result in recommendations.

Voluntary Participation

You contribution is highly valued, your participation in this research is entirely voluntary.

Procedures

We would like to ask you to participate in an interview with fellow professionals in the domain of nutrition or antimicrobial resistance.

You will receive a background for the interview, and a consent form. Please return this signed.

Before the interview, we would like to send you an invitation via ZOOM, in order for you to be able to participate from your own home or office environment.

Information recorded will be kept confidential; no one else except Erna Rijnierse and Saskia van der Kam will have access to the information documented during the interview. The interview will be recorded and the highlights of your contribution will be summarised and send back to you for your feedback and confirmation. The recording will be kept on my laptop, which is password-protected, to which no-one else has access. After the finalization of the thesis the recordings will be destroyed. The transcript will be made anonymously if you wish.

Confidentiality

For the sake of transparency and scientific scrutiny, I ask permission to use your name text and in quotes as appropriate, and mention your name and area of expertise in the list of interviewees. As alternative, when you indicate your wish, you can keep your contribution anonymous.

Right to Refuse or Withdraw

This is a reconfirmation that participation is voluntary and includes the right to withdraw. If at any given time or upon reading the report of the interview or panel discussion, you can review your remarks, and you can ask to modify or remove portions of those, if you do not agree with my notes or if I did not understand you correctly.

Duration

The interview will take about 1 hour of your time.

Risks

Your personal opinion and insights will be shared with a limited audience (KIT, MSF, and group of interviewed experts). The thesis might be spread beyond this group, specifically when the findings might inform programme strategies. To mitigate the unwanted spread of quotes from you side, the text with quotes is shared with you for your permission and review, before it will be final in the report.

Benefits

The direct benefit for you, is that you are able to contribute to this study and with that you are able to contribute to a possible change in the use of systematic antibiotics in the future, which will have an impact on costs and service delivery in future outpatient nutritional interventions.

Reimbursements

You will not be paid money to participate in this study. If you want to, we will provide you with a copy of the thesis upon completion.

Dissemination

The thesis will be shared with the KIT Royal Tropical Institute as well as with MSF nutrition working group. The results will also be shared with you.

Who to Contact

In case of questions on this informed consent form, Sandra Alba, of the Dutch Royal Tropical Institute in Amsterdam, is the co-chair of the ethical committee.

This study has been reviewed and received an ethical waiver from the KIT Research Ethics Committee, which is a committee whose task it is to make sure that research participants are protected from harm. If you wish to find about more about this, please contact S.Alba@kit.nl.

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions?

Part II: Certificate of Consent

I have been invited to participate in research about the systematic use of antibiotics in children 6 to 59 months old, with uncomplicated SAM in Sub Saharan Africa.

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions I have been asked have been answered to my satisfaction. I consent voluntarily to be a participant in this study.

Name of Participant: __________________________

Signature of Participant ____________________

Date ____________________________

Day/month/year

Statement by the researcher/person taking consent

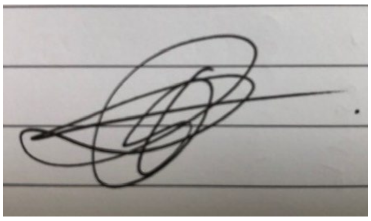
I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1. **Interviews are voluntarily and will be conducted and recorded**
2. **Information will be stored in confidential space**
3. **After completion of thesis, recordings will be destroyed**

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of the information sheet has been provided to the participant.

Name of Researcher/person taking the consent: Erna Rijnierse



Signature of Researcher /person taking the consent___________________________

Date _________________

ANNEX V: INTERVIEW QUESTIONS

1. Until now all children with uncomplicated SAM receive systematic antibiotics.
    a. Do you think that this is a good practice? Why, or why not?
    b. Would you consider to have an option to omit systematic antibiotics in certain contexts?
    c. If so what factors would play a role in deciding this?

2. What contextual factors could explain the difference in results of the research on the need of systematic antibiotics when comparing Ethiopia with Malawi and Niger?

3. More in general, contextual factors could be important in the decision of systematic antibiotic prescription
    a. Do you think there could be different recommendations for different contexts?
    b. Are some arguments more important than others?

4. Do situations of -a high of prevalence specific disease require a different approach from prescribing systematic antibiotics for SAM children in ambulatory settings, given that some of these illnesses are viral and unnecessary provision of antibiotics could increase AMR ?

5. Could the systematic antibiotic prescription depend for instance on a high prevalence of HIV? Diarrhoea? Upper respiratory tract infections? Measles outbreaks? Other prevailing illnesses?

6. Would you also consider to give medical staff f(predominantly nurses and community health workers) in an ATFC an option to omit or prescribe systematic antibiotics in certain indications/ conditions of the patient? If so what factors would play a role in deciding this?

7. In my experience, in areas where NGOs such as MSF or ACF work in a humanitarian context, the level of training of NGO staff exceeds the capacity of the ministry of health, often as training is an integrated part of starting nutritional programmes. Besides, these organisations have a more constant supply chain. There are also more referral options available.
    a. Do you think there could be different recommendations for different contexts even when a more favourable context is created by INGO's or other entities?

8. At the moment there are emerging food insecurity areas in Sub Saharan Africa. Would you consider different recommendations for specific emergencies which considerable malnutrition caused by predominantly food shortage?
    a. Food shortages alone?
    b. Food shortages combined with?? conflict or migration?

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