

Investigating the effect of interventional programmes in combatting inappropriate use of antibiotics in managing and treating acute gastroenteritis in children younger than five years at the Raleigh Fitkin Memorial Hospital in ESwatini

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DECLARATION

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ABSTRACT

Patients at the Raleigh Fitkin Memorial Hospital, ESwatini, especially children diagnosed with acute gastroenteritis, are mostly prescribed with antibiotics. Previous data suggest that inappropriate use of antibiotics results in higher antibiotic resistance, extended hospitalisation and increased medication costs. Antibiotic stewardship programmes and clinical practice guidelines can reduce the inappropriate use of antibiotics and improve patient outcomes. Despite increased theoretical awareness of the benefits of antibiotic stewardship programmes, none have been established in ESwatini, and limited comprehensive studies have evaluated their effect in paediatric settings globally. The knowledge, attitude and practices on antibiotic use and resistance have not been determined at the Raleigh Fitkin Memorial Hospital. An 18-month, single-centre process improvement study, comprising a six-month pre-intervention phase, a preparatory period of six months and a six-month intervention phase, was conducted at the Raleigh Fitkin Memorial Hospital to assess the effectiveness of a multifaceted intervention in combatting the inappropriate use of antibiotics and improving the management of acute gastroenteritis and its comorbidities in children aged less than five years. The intervention included the establishment of an antibiotic stewardship programme and the implementation of clinical practice guidelines related to the diagnosis, treatment and management of acute gastroenteritis and its associated comorbidities. Two hundred and thirteen patients participated in the study, with 87 patients in the pre-intervention phase and 126 in the intervention phase. Knowledge, attitude and practices of healthcare professionals were investigated by conducting a survey before and after the intervention phase. An improvement in the appropriateness of antibiotics use was observed in the intervention phase. A decrease in duration of hospitalisation, cost of antibiotics and mortality was observed. During the intervention phase, deaths were observed where severe acute malnutrition was present as comorbidity to acute gastroenteritis, whereas various causes of death were observed during the pre-intervention phase. Most recommendations by the antibiotic stewardship programme team were adopted during the intervention phase. An improvement in knowledge, attitude and practices on antibiotic use and resistance was observed after the intervention phase. The study demonstrates that an antibiotic stewardship programme can improve the appropriate use of antibiotics in children, with limited adverse effects. Clinical practice guidelines play a vital role in providing guidance to prescribers and harmonising therapies. Antibiotic stewardship programmes can improve healthcare professionals' knowledge, attitude and practices on the appropriate use of antibiotics, and a decrease in antibiotic resistance.

Keywords: Antibiotics; acute gastroenteritis; children; Raleigh Fitkin Memorial Hospital; antibiotic stewardship programme; ESwatini

OPSOMMING

Pasiënte by die Raleigh Fitkin Memorial-hospitaal in ESwatini, veral kinders wat gediagnoseer is met akute gastroenteritis, ontvang meestal antibiotika as voorskrif. Vroeër ingesamelde data dui daarop dat die onvanpaste gebruik van antibiotika lei tot groter antibiotiese weerstandigheid, langer hospitaalverblyf en verhoogde medikasiekoste. Antibiotiese bestuursprogramme en kliniese riglyne kan die onvanpaste gebruik van antibiotika verminder en die kliniese uitkomst van pasiënte verbeter. Ten spyte van toenemende teoretiese bewustheid van die voordele van antibiotiese bestuursprogramme, is geen sodanige program nog in ESwatini ingestel nie, en min omvattende studies het nog die effek daarvan in pediatriese omgewings wêreldwyd ondersoek. Die kennis, ingesteldheid en praktyke oor die gebruik van antibiotika en antibiotiese weerstandigheid is nog nie by die Raleigh Fitkin Memorial-hospitaal bepaal nie. 'n Agtien-maandelange enkelsentrum-prosesverbeteringstudie, bestaande uit 'n pre-intervensie-fase van ses maande, 'n voorbereidende periode van ses maande en 'n intervensie-fase van ses maande, is by die Raleigh Fitkin Memorial-hospitaal uitgevoer om die effektiwiteit van 'n multi-faset-intervensie vir die teenkamping van onvanpaste antibiotikagebruik en die verbetering van die bestuur van akute gastroënteritis en sy medemorbiditeite in kinders van jonger as vyf jaar, te evalueer. Die intervensie het die vestiging van 'n antibiotiese bestuursprogram en die implementering van kliniese riglyne vir die diagnose, behandeling en bestuur van akute gastroenteritis en sy geassosieerde medemorbiditeite ingesluit. 'n Totaal van 213 pasiënte is by die studie ingesluit, met 87 pasiënte in die pre-intervensie-fase 126 in die intervensie-fase. Die kennis, ingesteldheid en praktyke van professionele gesondheidsorgwerkers is ondersoek deur 'n opname voor en na die intervensie-fase uit te voer. 'n Verbetering in die gepastheid van antibiotikagebruik is waargeneem gedurende die intervensie-fase. 'n Afname in hospitaalverblyf, koste van antibiotika en sterftes is waargeneem. Gedurende die intervensie-fase is sterftes, was ernstige akute wanvoeding as medemorbiditeit van akute gastroenteritis teenwoordig was, terwyl verskillende oorsake vir sterftes gedurende die pre-intervensie-fase waargeneem is. Die meeste aanbevelings wat deur die antibiotiese bestuursprogram-span gemaak is, is aanvaar gedurende die intervensie-fase. 'n Verbetering in die kennis, ingesteldheid en praktyke oor die gebruik van antibiotika en antibiotiese weerstandigheid is waargeneem na die intervensie-fase. Die studie het gedemonstreer dat 'n antibiotiese bestuursprogram die gepastheid van antibiotika-gebruik in kinders kan verbeter, met beperkte klinies nadelige uitkomst. Kliniese riglyne speel 'n onontbeerlike rol om leiding aan voorskrywers te verskaf en om behandeling te harmoniseer. Antibiotiese bestuursprogramme kan professionele gesondheidswerkers se kennis, ingesteldheid en praktyke oor gepaste antibiotikagebruik verbeter en 'n afname in antibiotiese weerstandigheid tot gevolg hê.

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DISCLAIMER

This was a self-funded study. Any opinion, findings and conclusions or recommendations expressed in this material are those of the author(s).

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LIST OF ACRONYMS AND ABBREVIATIONS

AGE	Acute Gastroenteritis
APES	Academic and Professional Editing Services
ART	Anti-retroviral treatment
ARTI	Acute respiratory tract infections
ASC	Antibiotic stewardship committee
CAP	Community-acquired pneumonia
CDC	Centre of Disease Control
CMS	Central medical stores
CMV	Combined with a mineral vitamin
CRP	C - reactive protein
DOS	Days of stay
DOT	Days of therapy
DTC	Drugs and Therapeutics committee
EDHS	Ethiopian Demographic and Health Survey
EPEC	Enteropathogenic <i>E.coli</i>
ETEC	Enter toxigenic Escherichia coli
FIDSSA	Federation of Infectious Diseases Societies of Southern Africa
HREC	Health Research Ethics Committee

ICU	Intensive Care Unit
ID	Infectious disease
IDSA	Infectious Disease Society of America
IMAM	Integrated managing acute malnutrition
IPC	Infection and prevention control
LMIC	Low and middle-income countries
MCS	Microbiology, Culture & Sensitivity
MDG	Millennium Development Goals
MDR	Multi-drug-resistant
MGH	Mbabane Government Hospital
MOH	Ministry of Health
NHRRB	National Health Research Review Board
ORS	Oral Rehydration Salts
ORT	Oral rehydration therapy
PDR	Pan-drug-resistant
PIDS	Paediatric Infectious Disease Society
PO	Oral
QIP	Quality Improvement Project
RFMH	Raleigh Fitkin Memorial Hospital
SAASP	South African Antibiotic Stewardship Programme

SADC	Southern African Development Community
SAM	Severe Acute Malnutrition
SAMF	South African Medicine Formulary
SHEA	Society for Healthcare Epidemiology of America
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
SLIPTA	Stepwise Laboratory Quality Improvement Process towards Accreditation
SLMTA	Strengthening Laboratory Management towards Accreditation
SNNC	Swaziland National Nutrition Council
SOP	Standard Operation Procedure
SST	Serum Separator Tube
TDM	Therapeutic drug monitoring
TOR	Terms of reference
U&E	Urea and electrolytes
UK	United Kingdom
UNICEF	United Nations Children Funds
URTI	Upper Respiratory Tract Infections
US	United States
WHA	World Health Assembly
WHO	World Health Organisation
XLD	Xylose Lysine Deoxycholate

DEFINITIONS

Antibiotic: Any class of organic molecule that inhibits or kills microbes by specific interactions with bacterial targets, without any consideration of the source of the particular compound or class (Davies & Davies, 2010)

Antibiotic resistance: The ability of bacteria to grow in the presence of a substance (antibiotic) that would normally kill it or limit its growth (NIH, 2013).

Antibiotic stewardship programme: Coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting selecting the optimal [antibiotic] drug regimen including dosing, duration of therapy and route of administration (Fisherman, 2012)

Antibiotic stewardship committee: A multidisciplinary team that co-ordinates antimicrobial Stewardship Programmes (ASP). The committee mainly comprises specialised doctors, general practitioners, nurses, pharmacists and laboratory technologists (IDSA, 2007).

Diarrhoea: A passage of three or more loose or liquid stools per day, or more frequently than is normal for the individual. It is usually a symptom of gastrointestinal infection, which can be caused by a variety of bacterial, viral and parasitic organisms (WHO, 2013).

Susceptible (s): A bacterial strain ensues to be susceptible to a provided antibiotic when it is inhibited *in vitro* by a concentration of this drug associated with an elevated likelihood of therapeutic success (Rodloff *et al.*, 2008).

Intermediate (i): The sensitivity of a bacterial strain to a provided antibiotic ensues to be intermediate when it is inhibited *in vitro* by a concentration of this drug associated with an uncertain therapeutic effect (Rodloff *et al.*, 2018).

Resistant (r): A bacterial strain ensues to be resistant to a provided antibiotic when it is inhibited *in vitro* by a concentration of this drug associated with an elevated likelihood of therapeutic failure (Rodloff *et al.*, 2008).

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CHAPTER 1: INTRODUCTION

1.1 Problem statement

A study conducted by Matsebula-Myeni (2014) on the management and treatment of acute gastroenteritis (AGE) in children younger than five years, at the RFM Hospital, a tertiary hospital in Swaziland, indicated underutilisation of the ORS (Oral Rehydration Salts) therapy in managing dehydration, lack of bolus treatment with the correct fluids in severely dehydrated patients, overuse of intravenous therapy in dehydration management, inappropriate and overuse of antibiotics. Ninety-eight per cent of patients admitted, received at least one antibiotic throughout their admission stay, which was an average of seven days.

The most frequently used antibiotics were Ceftriaxone injections, Gentamycin injections, Metronidazole injections and Cefaclor suspensions (Matsebula-Myeni, 2014). This study concluded that there was an elevated and inappropriate use of antibiotics on AGE diagnosed children at the RFM Hospital and that the prescribers did not adhere to the 'Treating Diarrhea', a manual for physicians and other senior health workers (WHO, 2005) and the WHO recommendations on the 'Managing diarrhoea and pneumonia in HIV infected infants and children' (WHO, 2010). Benyera (2013) also revealed the overuse and inappropriate use of antibiotics in a study conducted in a referral hospital, Mbabane Government Hospital (MGH) in ESwatini, where an outpatient prescription survey revealed overusing antibiotics especially in Upper Respiratory Tract Infections (URTIs).

Even though, Systems for Improved Access to Pharmaceuticals and Services (SIAPS) programme in 2015, indicated a reduction in the percentage of prescriptions including at least one antibiotic from 59% to 52%, this rate remains higher than the WHO recommendation of 20-26% (SIAPS, February 2015). The results after implementing the STG, indicated a trend towards prescribing a higher number of antimicrobials for children and teenagers; prescriptions and the misuse of antibiotics was indicated. SIAPS emphasises that there was no intervention in-place to conflict the inappropriate use of antibiotics (SIAPS, February 2015). A small-scale Quality Improvement Project (QIP) conducted by the RFM Drugs and Therapeutics committee (DTC) indicated an elevated antibiotics resistance pattern (100% resistance to cotrimoxazole, 50% resistance to Ceftriaxone and 50% intermediate of Ceftriaxone) (Denhere *et al.*, 2015).

The limitation of QIP, is that the specific bacteria that were resistant to the antibiotics were not analysed, attributable to a lack of resources. It is possible that the resistance pattern observed could be caused by overusing these two antibiotics in the country.

The ample use of Ceftriaxone was discussed in various meetings at the RFM DTC's (Mavundla *et al.*, 2014; Mavundla *et al.*, 2015). Most prescribers alluded that Ceftriaxone is a safe, effective and an easily administered drug. The half-life of the antibiotic compared to the 1st and 2nd generation Cephalosporins enables nurses to administer it twice a day, which is convenient. The paediatrician also mentioned that the extensive use of Ceftriaxone was compelled because there was a time where it was the only available antibiotic from central medical stores (CMS). The prescribers had to use it for minor infections (Mavundla *et al.*, 2014).

Even though the Ministry of Health developed STGs, these guidelines were primarily intended for primary healthcare circumstance where there are no doctors available to issue prescriptions and nurses must fulfil the function of prescribers. The national STGs do not address acute gastroenteritis or dehydration in children intensively. The RFM Hospital does not have institutional clinical practice guidelines in-place that clearly address managing and treating AGE in children. This lack of clinical guidelines resulted in prescribing inconsistencies between the prescribers at the RFM Hospital, with prescribers tending to use their personal experience in treating AGE (Mavundla *et al.*, 2015). Principi & Esposito (2016), Berild *et al.* (2001) and Chandy *et al.* (2014) agree that clinical guidelines assist prescribers with appropriate decisions, improving consistency in prescribed medicines.

The RFM Hospital statistics data unit revealed that acute gastroenteritis (AGE), followed by SAM and pneumonia are the leading causes of death in children admitted at RFM Hospital (Dlamini, 2015). These statistics agree with the findings of various authors, considering AGE as a main cause of child mortality in the Sub-Saharan region (Hung, 2006; Ester *et al.*, 2011; Mengistie, Berhane & Worku, 2013; Brhanu, Negese & Gebrehiwot, 2017).

Although WHO guidelines (WHO, 2010) clearly guide prescribers to treat HIV positive children equal to HIV-negative children, prescribing trends at the RFM Hospital indicate that prescribers have an intense sense that HIV positive and HIV exposed children need to be protected with antibiotics. A study conducted by Eijk *et al.* (2009) in which the frequency and aetiology of diarrhoea in children aged less than two years in Kenya were compared, confirmed that there was no need to provide HIV positive children with antibiotics.

Most children admitted to the RFM Hospital with AGE as a primary diagnosis are also diagnosed with comorbidities (Matsebula-Myeni, 2014), which could render treating diarrhoea more complex. At the RFM Hospital the most frequently observed comorbidities of AGE, are malnutrition and pneumonia (Matsebula-Myeni, 2014; Dlamini, 2016). As there are currently no institutional practice guidelines for infectious diseases at the RFM Hospital, the frequent co-infection of AGE patients with pneumonia might lead to variable patient management amongst doctors and might also introduce inappropriate prescribing. This also applies to SAM. A national guideline on the integrated managing acute malnutrition (IMAM) was launched, printed and distributed by the Swaziland National Nutrition Council (SNNC) in 2013 (Vilakati *et al.*, 2013), but deaths of AGE with SAM as a comorbidity are still observed (Matsebula-Myeni, 2014).

Although this guideline is extensively available, the death rates for malnutrition in the RFM Hospital documented by its statistics unit (Dlamini, 2016), suggest that the guideline is not fully utilised. Similarly, Benyera (2013) established, at the MGH, a referral hospital in ESwatini, case fatality rates for childhood malnutrition remained extreme despite implementing the IMAM guideline (Vilakati *et al.*, 2013) at the hospital. From the 227 children who met the study inclusion criteria, 111 children passed away during admission, provided a case fatality rate of 40.1% (Benyera, 2013).

A further possible contributing factor to the inappropriate use of antibiotics is that the RFM Hospital lacks basic infrastructure and diagnostics tests. The hospital does not have an antibiogram; prescribers use their experience in selecting an empiric treatment for infectious diseases. The hospital lacks the availability of an infectious disease specialist and a pharmacist with an expertise in infectious diseases. Collectively these challenges compromised managing infection control, antibiotics use and containment of antimicrobial resistance in the hospital. Using antibiotics and the surveillance of antibiotic resistance in hospitals in ESwatini were deficiently quantified and no formal strategies were facilitated to optimise using antibiotics. Limited national capacity in ESwatini exists to identify and respond to urgent and emerging antibiotic resistance threats. Currently no systemic surveillance of antibiotic resistance threats exists in any of the country's hospitals, neither at clinics nor at tertiary level.

The lack of basic infrastructure and diagnostic tests in low and middle-income countries (LMICs) were noted as indicators of misdiagnosis and late diagnosis of infectious diseases (Cox *et al.*, 2017; Peeling and Mabey, 2010; Engel *et al.*, 2016, Sharma *et al.*, 2015). ESwatini has no accredited laboratory in the public sector that met the ISO 15189 standards that hampers the reliability of the cultures by the RFM Hospital. From personal observation during a meeting on appropriate use of antibiotics it appeared as if prescribers, nurses,

pharmacists and laboratory technologists worked in silos, with no formal and structured collaboration amongst the healthcare workers.

A contributing factor to the inappropriate use of antibiotics in the RFM Hospital could also be the lack of formal post-prescriptions audits. According to the study, no assessment was conducted to address the inappropriate use of antibiotics and antimicrobial resistance at RFM Hospital. Post-prescriptions audits proved to increase the appropriate use of antibiotics, reduce antibiotics' use and decrease restricted antibiotics (Boyles *et al.*, 2013; Brink *et al.*, 2016).

There is a proven link between excessive antibiotic use and increased resistance (Ho *et al.*, 2006; Smith & Coast, 2002; Ventola, 2015; Prigitano *et al.*, 2018). In response to this crisis, the 2015 World Health Assembly (WHA) adopted a global action plan on antibiotic resistance containment (WHA, 2015a). The global action plan had five objectives; two were to:

- Strengthen knowledge and evidence-based medicine through surveillance and research.
- Optimise using antibiotics in humans and animals (antimicrobial stewardship).

ESwatini does not have an official antimicrobial resistance containment strategy (ARCS); a committee is working on a draft National Action Plan.

It is with no doubt that if ESwatini does not improvise strategies to combat inappropriate use of antibiotics and contain antimicrobial resistance; the country may enter the pre-antibiotic era. The inappropriate use of antibiotics costs lives of several children and renders treatment of serious infections difficult, attributable to resistance. Overuse of antibiotics, especially intravenous antibiotics, unnecessarily increases the medicines and medical supplies budget.

1.2 Rationale of the study

RFM is a tertiary hospital with an elevated patient volume. There were no interventions constructed to inverse the inappropriate use of antibiotics in depth. Development of an ASP, specifically in paediatrics, is therefore proposed to improve using antibiotics. Antibiotic stewardship (ASP) is a multidimensional, multidisciplinary team approach to optimise antibiotic prescribing (Boyles *et al.*, 2013) and ASPs were

indicated to hold several benefits (Pate *et al.*, 2012; Cairns *et al.*, 2013; Berild *et al.*, 2001; Cisneros *et al.*, 2013)

Pate *et al.* (2012), facilitated an ASP at an urban hospital using a weekly post-prescriptive chart audit with intervention and feedback and for the fifteen first months; it demonstrated 80% acceptance of recommendations, a 21% reduction in use and a 28% reduction in cost per patient-day. An ASP interventional study by Cairns *et al.* (2013) yielded a 17% reduction in broad-spectrum antimicrobial use in the Intensive Care Unit (ICU) and a 10% reduction in broad-spectrum. Cairns *et al.* (2013) used the post-prescription audit, similar to the approach employed by Pate *et al.* (2012).

Berild *et al.* (2001) developed and facilitated clinical guidelines for antibiotic treatment and prophylaxis at Aker university Hospital. For over two years, there was a reduction of 11% in using antibiotics with a 23% reduction for broad-spectrum antibiotics. In agreement with the impact of guidelines observed by Berild *et al.* (2001), Chandy *et al.* (2014), a decline in using antibiotics as soon as a booklet of guideline implementation on antibiotics use was disseminated, used in a tertiary hospital in South India.

Cisneros *et al.* (2013) performed an educationally supported ASP, yielding a decrease of 26.4% of inappropriate antibiotics prescriptions and reflected a reduction in antimicrobial expenditure of 42%. Beardsley *et al.* (2012) demonstrated the monetary impact of ASPs over 11 years in the United States. It resulted in an average saving of \$920,070 to \$2,064,441 in antibiotic use outside the ICU setting, depending on the method of inflation adjustment.

An improvement in using antibiotics was reported in LMICs, despite the inadequacy of resources (Boyles *et al.*, 2016; Brink *et al.*, 2013; Cox *et al.*, 2013; Ho *et al.*, 2006; Mendelson, 2016). The authors documented similar successes, alike European countries (Brink *et al.*, 2013, Boyles *et al.*, 2016). Boyles *et al.* (2013) indicate that patient safety was not compromised by implementing an ASP in the clinical setting.

Brink *et al.* (2013), facilitated a pharmacist-compelled, prospective audit and feedback strategy for ASP based on a range of improvement science and behavioural principles amongst a diverse group of urban and rural private hospitals in South Africa. The ASP led to a reduction in mean antibiotic defined daily doses per 100 patient-days from 101.38 (95% CI 93.05-109.72) in the pre-implementation phase to 83.04 (74.87-91.22); in the post-implementation phase ($p < 0.0001$) (Brink *et al.*, 2013).

Boyles *et al.* (2016) facilitated an antibiotic prescription chart and weekly antibiotic stewardship ward rounds at two medical wards of an academic teaching hospital in South Africa. The patient database was analysed to determine inpatient mortality and 30-day readmission rates and laboratory records to determine usage of infection related tests. During the intervention there was a 19.6% decrease in antibiotic use with an antibiotic cost reduction of 35%. There was no difference in inpatient mortality or 30-day readmission rates during the control and intervention periods (Boyles *et al.*, 2016).

Based on these data and experiences, the need for a multifaceted intervention to manage and treat AGE in children at the RFM Hospital, was identified. The intervention should include proper diarrhoea and dehydration guidelines, antimicrobial prescribing guidelines and policies, restricting antibiotic use. To effectively overcome the inappropriate managing AGE and overusing antibiotics, close collaboration between doctors, pharmacists, nurses and laboratory staff was needed. The important function of a pharmacist in containing antimicrobial resistance, was supported in various studies performed in the United Kingdom (UK) (Waller & Jamieson, 2004, Knox *et al.*, 2002). Developing an ASP, led by a pharmacist, was proposed. The target population for this project were children aged less than five years, diagnosed with AGE as a primary diagnosis, where the inappropriate and overuse of antibiotics were documented at the RFM Hospital in an earlier study (Matsebula-Myeni, 2014).

Little is documented about knowledge, attitude and practice of healthcare professionals related to antibiotic use and resistance in ESwatini, including the RFM Hospital. It is therefore difficult to assess which type of behavioural intervention would best contribute to achieve the goal of appropriate use of antibiotics in the hospital.

Drawing strengths from the above literature, the research had confidence, introducing an ASP to be led by a pharmacist in a low resource tertiary. This research provided a baseline for implementing ASPs in ESwatini. On a broader scale, it can also serve as example for improving antibiotic use and containment of antimicrobial resistance in developing countries with limited resources.

1.3 Objectives and specific aims

1.3.1 Primary objective of the study

To establish an ASP at the RFM Hospital and to determine its effectiveness in combatting the inappropriate use of antibiotics and managing AGE and its comorbidities, targeting children less than five years old.

1.3.2 Specific aims

- **Specific Aim 1**

To reduce the overall and restricted antibiotic use, the proportion of inappropriate antibiotics used and to assess compliance with the (ASP) and patient outcomes.

- **Specific Aim 2**

To identify the bacterial cause of acute gastroenteritis, and the antibiotic sensitivity and resistance pattern of the bacterial isolates.

- **Specific Aim 3**

To develop and facilitate guidelines for managing SAM, antibiotic prescribing and the hydration protocol in children less than five years who present with acute gastroenteritis as a primary diagnosis.

1.3.3 Outcome measures of the primary objective

- Antibiotic utilisation: Decreased total and restricted antibiotic use per patient and decreased inappropriate antibiotics used.
- Process outcomes: High numbers of antibiotic stewardship recommendations adopted.
- Microbiological outcomes: Increased number of cultured bacteria and increased number of antibiotic sensitivity tests.
- Clinical outcomes: Reduced number of deaths and decreased hospitalisation days.
- Cost outcomes: Decreased cost of antibiotics.

- Adherence to clinical practice guidelines: Improved managing acute gastroenteritis and its comorbidities.

1.3.4 Secondary objective

To investigate the KAP of health care professionals related to antibiotic use and antibiotic resistance, to increase awareness and facilitate developing educational programmes and strategies for the appropriate use of antibiotics.

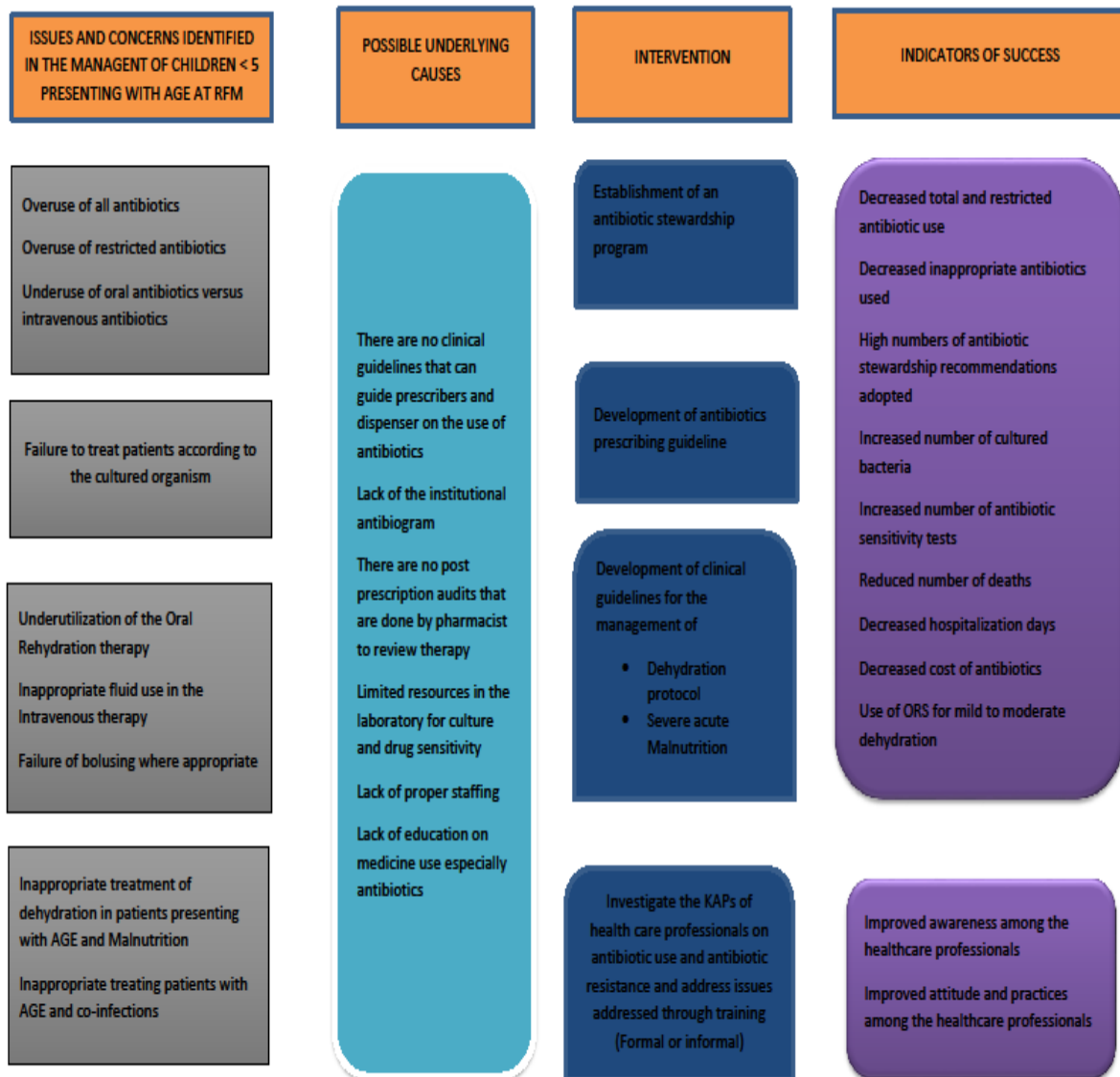
1.3.4.1 Outcome measures of the secondary objective

- Exploration: To investigate attitude and practices amongst health care professionals at RFM Hospital in prescribing and dispensing antibiotics.
- Test a hypothesis: To test if the interventional programmes to be put in-place, will have a positive effect in the KAP of healthcare professionals, by assessing antibiotic related issues amongst healthcare workers at RFM Hospital.
- Establish a baseline: To measure changes on antibiotics related knowledge and attitudes and to identify barriers to appropriate use of antibiotics.

1.4 Conceptual framework

The conceptual frameworks address challenges identified in the management and treatment of AGE in children less than five years at the RFM Hospital. The research was interested in addressing the challenges, causing inappropriate management of antibiotics at RFM Hospital. The research interest was also to construct interventions using the antimicrobial stewardship approach to address challenges faced by the hospital. The conceptual framework (Figure 1.1) addresses the challenge, the causes of challenges, the proposed intervention and the expected outcomes once the interventions are constructed.

Figure 1.1: Conceptual Framework, indicating management and treatment of acute gastroenteritis



CHAPTER 2: LITERATURE REVIEW

2.1 Definitions and diarrhoea types

Diarrhoea was a major public health problem in LMICs (Hung, 2006). It is amongst the leading causes of childhood morbidity and mortality in LMICs (Hung, 2006) and it is considered the second leading cause of death in children less than five years, especially in developing countries (Mengistie *et al.*, 2012). The startling situation is generated by delays in treatment initiation and inadequate hydration, resulting in high morbidity (Banerjee, Hazra & Bandyopadhyay, 2003).

The World Health Organisation (WHO) defines diarrhoea as the passage of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual), (WHO, 2017), whereas they do not consider frequent passing of formed stools as diarrhoea. Several authors used a similar definition of diarrhoea (Gracey, 1995; Hung, 2006; ESwatini, 2012; Nasser, 2014; Nasser, 2015; Armon *et al.*, 2001). Naseer (2014), defined it as an intestinal disorder characterised by abnormal fluidity and frequency of faecal evacuations, generally the result of increased motility in the colon.

The MOH, STG, for ESwatini defines diarrhoea as a condition characterised by loose or watery stools, three or more times in a day (ESwatini, 2012). The STG describes acute diarrhoea in the paediatric section as a watery, frequently stool occurring over three times a day, with no blood and lasting not more than 14 days. Acute diarrhoea usually is defined by an onset within 24 hours (Gracey, 1995). Hung (2006) describes diarrhoea in children as an excessive daily stool volume, more than the upper limit of around 10 g/kg/day (Hung 2006). Hung (2006) mentions that by this definition, it is possible to have diarrhoea with stools, at least partially formed. Diarrhoea results from an imbalance in the absorption and secretion properties of the intestinal tract; if absorption decreases or secretion increases beyond normal, diarrhoea results (Hung, 2006). Gracey (1996) addresses the difficulty usually experienced by nursing mothers in their ability to define a “normal stool” in a healthy infant. It often depends on perceptions of “normal”. Variations in infant stool patterns with some normal neonates passing up to six stools and some infants passing up to four stools daily, were observed (Gracey, 1995). Considering the history before diagnosing diarrhoea is important as breastfed infants pass more stools than other infants.

Diarrhoea may be classified into four conventional types, based on the mechanism, including osmotic diarrhoea, secretory diarrhoea, exudative diarrhoea and motility disorder diarrhoea (Hung 2006). Three clinical types of diarrhoeal disease were established, according to (WHO, 2017): Acute watery diarrhoea, acute bloody diarrhoea and persistent diarrhoea.

- Acute watery diarrhoea, which lasts several hours or days, may also include cholera. This term refers to diarrhoea characterised by abrupt onset of frequent, watery, loose stools without blood, lasting less than two weeks (Hung, 2006). It may be accompanied by flatulence, malaise, abdominal pain, nausea, vomiting and fever may be present.
- Acute bloody diarrhoea, also called dysentery, is defined as diarrhoea containing blood and mucus in faeces. Accompanying symptoms includes abdominal cramps, fever and rectal pain. The most compelling cause of bloody diarrhoea is *Shigella* (Hung, 2006). In developing countries, the main causative agents of dysentery are *S. flexneri*, *S. boydii* and *S. dysenteriae*.
- Persistent diarrhoea (14 days or longer) is defined as diarrhoeal episodes of assumed infectious aetiology with a long duration and last at least 14 days (Hung, 2006). About 10% of diarrhoea cases in children from developing countries become persistent, especially amongst those less than three years and more so amongst infants. The episode may begin acutely, either as watery diarrhoea or dysentery. This diarrhoea causes substantial weight loss in most patients (Hung, 2006). It may be responsible for about one-third to half of all diarrhoea-related deaths (Hung, 2006). Since persistent diarrhoea is a major cause of malnutrition in the developing countries, even the milder, non-fatal episodes contribute to the high mortality rates, frequently associated with malnutrition in these countries (Hung, 2006).

There are no published data on the relative probabilities of possible diagnoses in the child presenting to hospital with diarrhoea (Armon *et al.*, 2001). In the article Armon *et al.* (2001) emphasise that it was essential that the prescribers recognise any life-threatening causes of diarrhoea, such as intussusception and haemolytic uraemic syndrome (HUS). It is recommended that prescribers should observe causes of diarrhoea other than acute viral gastroenteritis for a child's diarrhoea with or without vomiting, which includes abdominal pain with tenderness, with or without guarding, pallor, jaundice, oligo/anuria, bloody diarrhoea, the patient being systemically unwell and a form proportional to the level of dehydration (Armon *et al.*, 2001).

2.2 The main causative agents of diarrhoea

Diarrhoea is considered as the most important public health challenge connected to deficient quality of water and sanitation (Hung, 2006). The same sentiments were shared by the MOH and STGs that the main causative of AGE is deficient hygiene (ESwatini, 2012).

Bacterial infections: In tropical and developing countries, diarrhoea is mostly caused by enteric bacterial infections (Gracey, 1995). It is a serious challenge amongst all ages from infancy to adults. The range of causative bacteria is significant and includes *E. coli*, *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *vibrio's* and *Clostridium difficile* (Hung, 2006; Gracey, 1995). Most of the episodes of diarrhoeal diseases that occur in children under five years of age, are attributable to pathogens that can be transmitted through food; pathogenic strains of *E. coli* are major proportions of the organisms involved (Gracey, 1995).

Viral infections: Viral infections is considered as the main cause of acute diarrhoea. Rotavirus is one of the most common causes of severe diarrhoea (Hung, 2006). Data retrieved from 34 studies on the aetiology of childhood gastroenteritis revealed rotavirus as the main detected causative of diarrhoea (71% of children; median = 33%) (Gracey 1995). There are other viruses that may be important causes of diarrhoeal disease in humans, including *Norwalk virus*, *Norwalk-like viruses*, *enteric adenoviruses*, *caliciviruses* and *astroviruses* (Hung, 2006).

Parasites: Parasites are considered as the leading cause of diarrhoea in developing countries with deficient hygiene and sanitation (Gracey, 1995; Hung, 2006). Parasites can enter the body through food or water and settle in the digestive system. Parasites due to diarrhoea, include *Giardia lamblia*, *Entamoeba histolytica*, *Cyclospora cayetanensis* and *Cryptosporidium* (Hung, 2006).

Food intolerance: Some individuals cannot digest certain components of food, such as lactose, the sugar established in milk, or gluten in wheat and barley (Hung, 2006).

2.3 Risk factors for diarrhoea

Children residing in rural areas were established to be more likely to be suffering from diarrhoea compared to those in the urban areas (Brhanu *et al.*, 2017). Studies indicated that the prevalence of diarrhoea is higher in younger children (Hung, 2006; Oloruntoba *et al.*, 2014; Kabayiza, 2014) and females experience more episodes of diarrhoea than males (Banerjee, Hazra & Bandyopadhyay, 2004). The prevalence is highest for children six to eleven months of age, remains at a high-level amongst one-year old children and decreases in the third and fourth years of life (Brhanu *et al.*, 2017). The statistics regarding the age-related prevalence of diarrhoea is in agreement with several studies (Brhanu *et al.*, 2017; Hung 2006; Banerjee, Hazra & Bandyopadhyay, 2004 and Kabayiza, 2014). Boys have a higher rate of diarrhoea compared to girls (Muhsen *et al.*, 2017; Staat *et al.*, 1991; Siziya, Muula & Rudatsikira, 2013). Contrary to what other studies revealed about males being the most affected by diarrhoea (Banerjee, Hazra & Bandyopadhyay, 2014 and Thiam *et al.*, 2017) in Senegal it is revealed that “female children suffered more than males in all the three areas, but none were established to be statistically significant”.

A study by (Maphalala *et al.*, 2017) in two sentimental hospitals (RFM Hospital and MGH) revealed 50.5% males and 49.5% females below the age of five years were admitted for managing acute gastroenteritis (AGE) (Maphalala *et al.*, 2017). Other important demographic factors, such as mothers’ age, level of mother's education, number of siblings, birth order, are significantly associated with a higher occurrence of diarrhoea in children less than five (Hung, 2006). Brhanu *et al.* (2017) agreed with Hung (2006) that children of mothers with a low level of education experience more episodes of diarrhoea, compared to children born from mothers with a higher level of education. Brhanu *et al.* (2017) also emphasised that maternal child care is important, contributing to diarrhoeal disease morbidity. This might be explained because maternal morbidity is considered as a sign of disease exposure in a family as mothers are the food handlers of the family and they are usually the main child care providers (Brhanu *et al.*, 2017).

Most children compared to adults, die annually from diseases directly linked to a lack of basic hygiene (UNICEF, 2007). Action relating to sanitation, hygiene and water supply indicated that it is possible to reduce the frequency, severity and economic impact of disease (WASH, 2007). Sanitation obviously partakes a crucial function in reducing diarrhoea morbidity (Oloruntoba *et al.*, 2014). Some sanitation factors, like improper disposal of children's stool, non-existence of toilettes or unhygienic toilettes and sharing such, increased the

risk for diarrhoea in children (Oloruntoba *et al.*, 2014; Brhanu *et al.*, 2017). Some studies revealed that children not washing hand before meals or after defecation, mothers not washing hands before feeding children or preparing foods, dirty feeding bottles and utensils and unhygienic domestic places (kitchen, living room, yard), were associated with the risk of diarrhoea morbidity in children (Hung, 2006).

Water-related factors are important determinants of the occurrence of diarrhoea, as diarrhoea is acquired through contaminated water and foods (Hung, 2006). This view agrees with Brhanu *et al.*, 2017; Oloruntoba *et al.*, 2014). Brhanu *et al.* (2017), in a study conducted in Ethiopia observed that drinking water treated at home was a forecaster of diarrhoeal morbidity. Factors that would contribute to the latter, were that contamination during collection, transportation and storage, which may in turn increase risk of diarrhoeal diseases. Their results contradicted a study in the same country by Anteneh & Kumie (2010) where they conclude that mere pit toilet utilisation did not contribute to the impact of the occurrence of childhood diarrhoea.

In 2000, a team of WHO experts clearly established that breastfeeding protects babies against the risks of diarrhoeic infections. The influence of breastfeeding on the prevention of infant mortality existed, which led to a recommendation for a six-month period of breastfeeding (WHO, 2000). The literature on feeding practices and risk of diarrhoea is extensive (Hung, 2006; Brhanu *et al.*, 2017); Botswana, 2012; Beck, 2007; Gizaw *et al.*, 2017). Several studies indicated the strong protective effect of breastfeeding (Gizaw *et al.*, 2017; Ogbo *et al.*, 2017; Sharma *et al.*, 2017). In general, the morbidity of diarrhoea is the lowest in exclusively breastfed children; it is higher in partially breastfed children and highest in fully-weaned children (Hung, 2006; Bener, 2011; Acharyaa *et al.*, 2017). The authors also indicated evidence that breastfed children with diarrhoea, should continue being breastfed throughout the rehydration and maintenance phases. The risk of dehydration is reduced; the children pass smaller volumes of stool and recover speedier (Armon *et al.*, 2003). A particular risk of diarrhoea is associated with bottle-feeding (Gribble & Hausman, 2012). Ziyane (1996) alluded, infant mortality is high in ESwatini (98/1000). She quoted studies that contributed to the infant mortality. About 70% of infant deaths occur before the age of six months (UNICEF, 1994). In this age group, early infant death, is attributable to deficient feeding practices; that is introduction of breast milk substitutes at one to two months of age (Friedman, 1991). In ESwatini, exclusive breastfeeding for six months is as low as 8% (Ziyane, 1996); early supplements, comprising cereals, maize and sorghum gruel is widespread even in rural areas; diarrhoeal mortality is 15% amongst infants (Ziyane, 1996).

Diarrhoea can be considered as a source and consequence of malnutrition (UNICEF, 2007). Diarrhoea prevents children from achieving their normal growth, whilst it increases the frequency and the duration of diarrhoeic events, creating a vicious circle (UNICEF, 2007). Malnutrition is the underlying cause for the increased susceptibility to infections and is indirectly responsible for several child deaths (Reddy *et al.*, 2016). The association between diarrhoea and malnutrition is common in low-middle-income countries (Hung, 2006; Brhanu *et al.*, 2017; Ferdous *et al.*, 2013). Ferdous *et al.* (2013) further alluded that the association between malnutrition and diarrheal mortality is bidirectional and was reported for decades as an association between diarrhoea and deficient growth and development of young children. Children whose immune systems were weakened by malnutrition, are the most vulnerable to diarrhoea (Hung, 2006; Brhanu, 2017, Ferdous *et al.*, 2013). The same sentiment is shared by Gracey (1995). Specifically, persistent and chronic diarrhoea, undermines nutritional status, resulting in malabsorption of nutrients or the inability to use nutrients properly to maintain health (Hung, 2006; Ferdous *et al.*, 2013).

Several studies reported higher incidences of diarrhoea in malnourished children (Hung, 2006; Ferdous *et al.*, 2013; Gupta, 2014; Irena *et al.*, 2011, Guerrant *et al.*, 1992). These studies by Ferdous *et al.* (2013) and Gupta (2014), indicate a tendency of increased incidence of diarrhoea, also established in children with low weight-for-age, in developing countries. Elliot (2007) mention that children with deficient nutrition are at an increased risk of complications and that developing parts of Australia have increased rates of admission for gastroenteritis, malnutrition, comorbidity and electrolyte disturbance (especially hypokalaemia) and a longer hospitalisation than the developed parts of Australia. This finding is coherent with Quiroga (2011), who established that malnutrition is the fundamental cause of 53% of all deaths amongst children under five, globally and established that the frequency of infectious disease as the basic cause of death was seven times higher when malnutrition coexisted as antecedent cause. Rice (2000) and Ahmend (2001) concur that children with severe malnutrition and diarrhoea have high mortality rates, some were previously attributed to faulty case-management.

Immunodeficiency is not only a cause of persistent or chronic diarrhoea but also a risk factor for diarrhoea (Hung, 2006). Attributable to acquired immunodeficiency, patients are exposed to pathogens causing infectious diseases, including diarrhoea Pavlinac *et al.* (2015). Diarrhoeal incidence, duration, severity and mortality are higher in children with HIV/AIDS than in others (Pavlinac *et al.*, 2015).

The incidence of diarrhoeal diseases varies with the seasons and a child's age. The youngest children are most vulnerable with incidence been highest in the first two years of life although this declines as the child grow older (Oloruntoba *et al.*, 2014). Seasonal patterns to childhood diarrhoea were noted in several tropical locations (Hung, 2006; Oloruntoba *et al.*, 2016) where there are two definite seasonal peaks: summer (associated with bacterial infections) and winter, related to viruses. In some studies diarrhoea prevalence was established to be higher in the rainy season than in the dry season (Hung, 2006).

The global and African burden of diarrhoeal disease in children

Infectious diarrhoea remains one of the leading causes of childhood morbidity and mortality global (Gracey, 1995; Brhanu, 2017) and cases of diarrhoea still occur in children despite government-oriented interventions (Oloruntoba *et al.*, 2014). According to the WHO and United Nations Children Funds (UNICEF) there are about two billion cases of diarrhoeal diseases global annually (Brhanu, 2017), which increased from the estimation made by (Hung, 2006), where episodes of diarrhoea were estimated at one billion, with 2.5 million deaths occurring each year amongst children under five years of age (Hung, 2006) and the 1.5 million deaths annually in children under five years of age, estimated by Mengistie (2012). Diarrhoea kills over 5,000 under five children daily-more than AIDS, malaria and measles combined, one in nine under five child deaths are attributable to diarrhoea (Mengistie, 2012; Brhanu, 2017). Whilst diarrhoeal disease occurs global, 90% of diarrhoeal disease deaths in under five children occur in developing countries, of which about 80% of deaths, attributable to diarrhoea occur in the first two years of life (Hung, 2006).

According to an Ethiopian Demographic and Health Survey (EDHS) conducted in 2011, the prevalence of diarrhoea amongst under five children is 13% (Brhanu 2017) and it is the leading cause of death in Nigeria (Oloruntoba *et al.*, 2014). Approximately one million neonatal deaths annually are caused by infection, Waet *al. et al* (2011) claiming over 25% of global neonatal deaths and about 10% of all mortality in infants under the age of five years.

Illness and death from childhood pneumonia and diarrhoea indicated a global walker *et al*, 2013) and a diarrhoea and pneumonia progress report by John Hopkins (2016) revealed that pneumonia and diarrhoea mortality in young children continued to be disproportionately concentrated in a few countries, year after year and the number of episodes were falling, but action is required global and at country level to accelerate the

reduction. In 2015, in ESwatini there were 230 deaths, attributable to diarrhoea, which contributed to 10% of the mortality for children under five years in ESwatini (Times of ESwatini, 2014:p3).

Diarrhoeal disease remains a primary cause of death and ill health of children in Sub-Saharan Africa, a region where economic, geographic, political, personal and sociocultural factors cooperate to create ongoing challenges to its prevention and control (Hamer *et al.* 1998). Despite the measures that were put in-place in ESwatini a progress report by UNICEF (2017) revealed that diarrhoea contributes 10-15% to childhood deaths. There was an expectation that diarrhoeal diseases would decrease by 25% over a year in Sub-Saharan African (Hamer *et al.* 1998) but the change has not been seen. The same sentiment was still shared by recent study with indicated that the introduction of vaccination e.g. rotavirus has not changed the global burden of diarrhoea, Mokomane *et al.* (2018).

According to the hospital statistical unit, diarrhoeal diseases remain the leading cause of hospitalisation of children less than five years old (RFM, 2016). In 2014 a rotavirus immunisation campaign was performed for all children under two years in ESwatini to decrease the incidence of diarrhoea, attributable to rotavirus but a significant difference has not been observed yet. In ESwatini, the prevalence of rotavirus was not known until a study was performed between January 2013 - December 2014. All the children that were hospitalised had stool samples collected and 302 (91%) were tested for rotavirus and 159 (52.6%) were positive for rotavirus (Maphalala *et al.*, 2017).

2.4 Prevention and control of diarrhoea

The WHO, Control of Diarrheal Diseases (CDC) programme and other organisations, including UNICEF and USAID (United States Agency for Global Development) provided priority to the prevention of diarrhoeal deaths, rather than prevention of cases and focussed on promotion of oral rehydration therapy (ORT) (Hung, 2006). Morbidity and mortality in diarrhoea is mainly attributable to severe dehydration (Banerjee, Hazra & Bandyopadhyay, 2004). The latter author discussed the importance of ORT in prevention and managing severe diarrhoea. He alluded, initiation of this therapy is crucial for its efficacy. The same managing diarrhoea was emphasised by Mengistie (2012) when he mentioned that ORT is a primary intervention for managing diarrhoea and it has an advantage of easy administration and being simple and affordable.

A long-term, sustainable solution to childhood diarrhoeal disease must combine treatment with actions to eliminate diarrhoeal disease through prevention (Hung, 2006). A consensus developed that the crucial factors for the prevention of diarrhoea are sanitation, personal hygiene, availability of decent quality drinking water (Hung, 2006). Developing countries documented promoting breastfeeding, ORT and specific health education as part of national strategies, aiming to improve the quality of life and reduce the burdens caused by diarrhoea (Hung, 2006; Sharma *et al.*, 2017; Bener *et al.*, 2011).

2.5 Treatment of diarrhoea

Several variations in managing acute diarrhoea especially in children were observed in various countries. Armon *et al.* (2001) developed an evidence and consensus-based guideline for managing children, admitted to hospital with diarrhoea. The aims of the guideline were to (1) to improve the process and outcome of care for children attending hospital with diarrhoea; (2) to promote consistency of care, allowing patients with almost identical clinical challenges to be managed in the same way; and (3) to inform, educate and improve the clinical decision-making of the junior clinicians, consulting with most of these children initially.

The goal of treating diarrhoea is to maintain hydration, treat the underlying causes and relieve the symptoms of diarrhoea (Hung, 2006). According to Armon *et al.* (2003), managing gastroenteritis, comprises correction of dehydration and maintenance of hydration; it is important to accurately estimate the level of dehydration. Rehydration and the correction of any electrolyte imbalance are critical in treating diarrhoea. Armon *et al.* (2001) mentioned researchers (Duggan *et al.*, 1996; Mackenzie *et al.*, 1989) who agreed about the proper diagnosis of dehydration, based on “prolonged skinfold”, “dry oral mucosa”, “sunken eyes” and “altered neurological status” These symptoms represented the most appropriate clinical signs correlating with dehydration as determined by post-rehydration weight gain. The authors also mentioned the important laboratory diagnostics of a urea of >6.5 mmol/l in a serum blood sample and pH<7.35 on blood gas as positive investigations associated with dehydration. The sensitivity and specificity of all these signs were low (Armon *et al.*, 2001). Symptomatic relief is a second therapeutic goal (Hung, 2006).

ORT was introduced in the past decades and rapidly became the gold standard of the CDD programme (Hung, 2006; Mengistie *et al.*, 2012). This therapy is achievable, efficient and safe in hospital treatment and at the primary care level in developing countries, preventing metabolic complications of diarrhoea and dehydration,

whilst reducing hospitalisation (Gracey, 1995). Proper utilisation of ORS can save the cost of requesting serum electrolytes from the laboratory, as ORS with the appropriate amounts of solutes and provided in the correct quantity is sufficient to correct electrolyte abnormalities (Armon *et al.*, 2001). Armon *et al.* (2001) further mention that there was no direct evidence indicating when serum electrolytes should be measured in a child with diarrhoea, especially when the rehydration would be treated with ORS. They quoted a study of cohorts of children in the UK with gastroenteritis, indicating that derangement of electrolytes was rare with 1% of admissions suffering from hypernatraemia; there were no reports of hypokalaemia or hyponatraemia.

Urea and electrolytes (U&E) should be measured in children receiving intravenous rehydration therapy, as hypernatraemia will alter with the rate at which intravenous rehydration fluids are provided; further measurements of U&E should be made as rehydration progresses (Armon *et al.*, 2001). There should also be a consideration for dehydrated children whose history or physical findings are inconsistent with simple diarrhoeal episodes and where a “doughy” sense to the skin may indicate hypernatraemia (Armon *et al.*, 2001).

Even though the successes of ORT and intravenous fluid treatments were documented, and much attention was provided over the last decade on proper managing acute diarrhoea, this had inefficient impact on the prevention of deaths from diarrhoea (Banerjee, Hazra & Bandyopadhyay, 2003). The therapy is not accepted well in developed countries, where there may be widely-held perceptions that intravenous fluids are usually needed in children with acute diarrheal episodes (Mengistie *et al.*, 2012). It is gradually becoming accepted in the developing countries, although it was referred to as “the under-used simple solution” because of the resistance of paediatricians (Gracey, 1995).

Evidence exists from several randomised controlled trials, that anti-diarrhoeal and antimotility medicines are not clinically beneficial in managing AGE in children. Their side-effect profiles are unacceptable (Armon *et al.*, 2003). Symptomatic anti-diarrhoeal drugs are usually not recommended for treating acute diarrhoea in children (Gracey, 1995; Hung, 2006). Antimicrobials are ineffective in uncomplicated acute diarrhoea and their use should be discouraged (Mokomane *et al.*, 2018). In contrast, antimicrobials are indicated in dysentery, cholera, typhoid fever and diarrhoea caused by parasites, such as *Giardia lamblia*, *Cyclospora* and *E. histolytic* (Hung, 2006). The reasons why antibiotics are not recommended in childhood gastroenteritis, include some episodes (e.g. those caused by viruses) would not respond to antibiotics; several enteric

bacteria are antibiotic-resistant; unselective usage of antibiotics encourages developing plasmid-transmitted drug resistance; and antibiotic treatment can prolong carriage for some microorganisms, such as *Salmonella* (Gracey, 1995). Antibiotics are expensive and have significant side effects. Antibiotics may be indicated for medical reasons, such as treatment of a coexistent respiratory infection or serious infections, particularly in young, small or compromised infants and young children (Gracey, 1995).

2.5.1 Global situational analysis: Antimicrobial use and antimicrobial resistance

An initial “country situation analysis” was conducted in 2013 in Member States in each of the six WHO regions to determine the extent to which effective practices and structures, addressing antimicrobial resistance are already in-place and where divergences remain; only a few countries reported having a comprehensive national plan based on a multisectoral approach, with sustainable financing (WHO, 2013).

A Global Point Prevalence Survey (Global-PPS) of a global network of 303 hospitals in 53 countries was established. The aim was to measure global antimicrobial prescribing and resistance, assessing antimicrobial prescribing and resistance in hospital inpatients, including eight lower middle-income and seventeen upper-middle-income countries. The survey revealed that 34.4% of patients received at least one antimicrobial, of which 89.3% were antibacterial agents for systemic use. The top three antibiotics prescribed globally, were penicillin with β -lactamase inhibitors, third-generation Cephalosporins and fluoroquinolones (Versporten *et al.*, 2018).

A neonatal and paediatric antimicrobial PPS of the Antibiotic Resistance and Prescribing in a European children project was held. Seventy-three hospitals (European and non-European) were recruited in the study on a one-day PPS on antimicrobial use in hospitalised children in September 2011. The study revealed that antibiotic paediatric and neonatal use was significantly higher in non-European patients (43.8%; 95% confidence interval [CI]: 41.3-46.3% and 39.4%; 95% CI: 35.5-43.4%) compared with that in European hospitals (35.4; 95% CI: 33.6-37.2% and 21.8%; 95% CI: 19.4-24.2%) Versporten *et al.* (2013).

A PPS assessing patterns of antibiotic use in a leading referral hospital in Western Kenya, revealed that 67.7% patients were on antibiotics. The most common classes of antibiotics prescribed were third-generation Cephalosporins (55%), imidazole derivatives like Metronidazole (41.8%) and broad-spectrum penicillin

(41.8%) (Okotho *et al.*, 2018). Another PPS study by Labi *et al.* (2018) in a tertiary hospital in Ghana, indicated that of the 677 inpatients surveyed, 348 (51.4%, 95% CI, 47.6-55.2) were on treatment with antibiotics. Prevalence was highest amongst paediatric surgery where 20/22 patients (90.9%, 95% CI, 70.8-98.9) were administered antibiotics and lowest amongst obstetrics patients with 77/214 (36%, 95% CI, 29.5-42.8) (Labi *et al.*, 2018). The top five antibiotics prescribed in the hospital, were Metronidazole 107 (17.5%), amoxicillin-clavulanic acid 82 (13.4%), Ceftriaxone 17(12.1%), Cefuroxime 61 (10.0%) and cloxacillin 52 (8.5%) respectively. Most patients. 181 (52%) were treated with two antibiotics (Labi *et al.*, 2018).

Concerning antibiotic consumption, South Africa was recently emphasised as a major contributor to the global increase in antibiotic use (Mendelson & Matsoso, 2016). Despite the need to quantify the misuse of antibiotics at provincial, local, district and institutional levels, no integrated information systems linking Pharmacy with laboratory and clinical data are prepared (Mendelson & Matsoso, 2016). Koopmans *et al.* (2018) performed a study at hospital level, evaluating antimicrobial consumption rates, the antimicrobial spectrum used and the indications for therapy on a paediatric ward and at the paediatric ICU (PICU) at the Tygerberg Hospital, Cape Town, South Africa. From the 703 patients admitted during the six-month study period, 415/451 (92%) paediatric ward admissions and 233/252 (92%) PICU admissions received antimicrobials (Koopmans *et al.*, (018). In the ward, 89% of prescriptions were for community-acquired infections. Ampicillin and third-generation Cephalosporins were the most commonly prescribed agents, Koopmans *et al.* (2018).

2.5.2 The significance of antibiotic resistance and other adverse outcomes

‘Antimicrobial resistance threatens the achievement of the Sustainable Development Goals and requires a global response’ (TIMES, 2016). This statement brought by one UN member states (Mr Thomas) indicates the significance of antimicrobial resistance globally. The level of threat to the health, social and economic aspects was signified because ‘this was for the first time, Heads of State committed to taking a broad, coordinated approach to address the root causes of AMR across multiple sectors, especially human health, animal health and agriculture’ (TIMES, 2017). This was the fourth time a health issue was considered by the UN General Assembly at a high-level meeting of the 71 sessions of the UN General Assembly (the others were HIV, non-communicable diseases and Ebola) (TIMES, 2017).

Bacterial resistance to antibiotics became a global threat, especially in LMICs (Laxminarayan *et al.*, 2014). Antibiotics are extensively used, but their value in the clinical setting is decreased by the increase in antibiotic-resistance bacteria (Ho *et al.*, 2006). The United States Centers for Disease Control and Prevention (US CDC, 2015) estimated that about 2 million illnesses in the US were caused by antimicrobial resistance, which claims approximately 23 000 deaths annually (US CDC, 2015). These alarming figures of deaths, attributable to antimicrobial resistance are caused by the indiscriminate and overuse of antimicrobial agents within hospitals (Ho *et al.*, 2006). Antibiotic resistance (ABR) is a critical threat to public health globally. If it would not be considered as serious, it could result in 10 million deaths annually, at a cumulative cost of USD 100 trillion by 2050 (Brink *et al.*, 2016).

The true burden of bacterial infection in South Africa remains incompletely documented, attributable to a high-level of empiric management and a paucity of samples sent for laboratory diagnosis (Mendelson, 2016). This is also true for ESwatini as the burden of antibiotic resistance were not understood with the only documented and published instance of resistance being multi-drug-resistant tuberculosis (Sanchez-Padilla *et al.*, 2012). The ESwatini National AIDS Programme, in collaboration with the Ministry of Health, adopted cotrimoxazole as an opportunistic disease prophylaxis (MOH, 2010). It follows, that with such an elevated burden of infection, an equally high burden of antimicrobial use occurs and hence, antimicrobial resistance (Mendelson, 2016).

The extensive use of cotrimoxazole can be attributed to the cotrimoxazole prophylaxis introduced by the ESwatini Integrated HIV guidelines in 2010 (National Comprehensive HIV Care, 2010) requiring all patients with HIV infection, including those on anti-retroviral treatment (ART) to receive cotrimoxazole prophylaxis. In ESwatini, there is no published research that evaluated the benefit of the cotrimoxazole prophylaxis, but an observational cohort study of five-year follow-up by Badri *et al.* (2001), performed in adult HIV clinics in South Africa, evaluated the proposed WHO/UNAIDS criteria for initiating cotrimoxazole prophylaxis in adult HIV-infected patients in Africa. This is stipulated in the guidelines on post-exposure prophylaxis for HIV and using cotrimoxazole prophylaxis for HIV-related infections amongst adults, adolescents and children (WHO, 2014). Even though it reduced mortality [adjusted hazard ratio (AHR), 0.56; 95% confidence interval (CI), 0.33-0.85; $P > 0.001$] and the incidence of severe HIV-related illnesses, the authors alluded that studies are needed to assess the optimal time to commencement of prophylaxis, as prevalent cotrimoxazole use will lead to increasing antimicrobial resistance to other major pathogens in Africa (Badri *et al.*, 2001).

According to Laxminarayan *et al.* (2012) using cotrimoxazole to treat opportunistic infections increased resistance to cotrimoxazole in *Pneumococci* and *E.coli*. From observations in using antibiotics, it is increased by the lack of stringent laws. Private pharmacies dispense antibiotics to patients without prescription from prescribers and even if prescribers wrongly prescribe antibiotics, the Pharmacy personnel dispense the medication to patients (Laxminarayan *et al.*, 2012).

Laxminarayan *et al.* (2012) state that in certain developing countries (Nigeria and Sudan), up to 90% of antibiotics are available over the counter without a prescription. Non-prescription transactions are common in almost all countries; these findings are consistent with reports (WHO, 2010) that over 50% of antibiotics globally, are purchased privately without a prescription, from pharmacies or street vendors in the informal sector. Self-medication was noted in the United States of America and Europe, particularly for colds and upper respiratory tract symptoms, self-limiting and mostly caused by viruses (WHO, 2010). South Africa initiated a national public surveillance programme for bacteria causing specific respiratory, gastrointestinal and central nervous system infections, but there are significant divergences in knowledge about drug resistance in bacteria, other than tuberculosis (hereafter termed bacterial resistance) (Mendelson, 2016).

Whilst developing new antibiotics for gram-positive infections could persevere the emergence of resistant bacteria, this is not the same for antibiotics against gram-negative infections, with none expected on the market for the next decade (Boyles *et al.*, 2013). The alarming increase in rates of extended spectrum beta-lactamase (ESBL)-producing gram-negative bacteria being reported from South African hospitals (Boyles *et al.*, 2013) and countrywide outbreaks of Carbapenems-Resistant Enterobacteriaceae, is a sincere concern (Boyles *et al.*, 2013). Compounding the challenge is the lack of infection prevention control capacity in South Africa, rendering it difficult to contain the spread of resistant bacterial infections. It poses a direct threat to patient safety (Boyles *et al.*, 2013). Although antimicrobial resistance data were not collected for ESwatini, a situation similar to that in South Africa (Boyles *et al.*, 2013) is believed to exist in ESwatini. The two countries are direct neighbours and travelling between the two countries occurs regularly and without the need for a visa.

Cost containment is often the overriding priority in managing patient, but with the rapid development and dissemination of multi-resistant organism in the hospital settings, global attention is now firmly engrossed on controlling antibiotic use to pause the increase and spread of such organisms (Knox *et al.*, 2003). In a four-

year study conducted by Boyles *et al.* (2017), there was an inflation-adjusted cost of antibiotics of ZAR 2,191,594 in 2011 and lower, for each of the subsequent years. By 2015, inflation-adjusted cost was 46% lower than in 2011. The total savings over the four years was ZAR3 263 340 (Boyles *et al.*, 2017). This finding suggests that ASPs cannot only fund themselves but can potentially be a source of revenue to provide infection prevention and quality improvement programmes advancing patient safety, related to infection (Boyles *et al.*, 2017).

Healthcare associated infections (HCAIs) are also progressively documented in LMICs. A recent evaluation revealed that the collective occurrence of HCAIs in resource-limited settings was twice the average prevalence of HCAIs in Europe (Laxminarayan *et al.*, 2014). HCAIs are mainly associated with the increased use of antibiotics, as they may worsen a patient's clinical outcome and prolong hospitalisation (Bebella & Muiruc, 2014). Equally, the necessity for antibiotics and the burden of resistance are likely to upsurge with the rate of HCAIs in LMICs (Laxminarayan *et al.*, 2014). The susceptibility to infections, especially in children, can be attributed to the poverty status encountering LMICs in the Sub-Saharan region. Impervious infections are costly to treat. Patients infected with resistant strains of bacteria are likely to need prolonged hospitalisation, which would increase costs, compared to patients infected with drug-susceptible strains, which need affordable and readily available first-line treatment and a shorter hospital admission (Laxminarayan *et al.*, 2014).

A previous study on children at RFMH did not quantify antibiotic resistance (Matsebula-Myeni, 2015). A correlation between resistance and mortality is challenging to demonstrate because the risk influences for infection with a resistant pathogen, including duration of hospitalisation especially in an ICU, are similar to those causing inferior outcomes in patients without resistant pathogens (Fortin *et al.*, 2015). Allerberger *et al.* (2008) state that if antimicrobial agents continue with an alarming resistance rate, it is possible to establish the return of the pre-antibiotic era or conversely, the emergence of the post-antibiotic era. This was echoed by Barriere (2014) who emphasises that the possibility of the return to a pre-antibiotic era, where ill health and death rates could rise dramatically. Routine surgical procedures would not be performed for fear of post-operative infections.

The inappropriate and overuse of antibiotics have numerous negative consequences, including significantly increased incidences of drug-related adverse events (Principi *et al.*, 2016) threatening public health

(Goossens *et al.*, 2006). Brink *et al.* (2016) mention that overuse and inappropriate use of antibiotics resulted in the emergence of multi-drug-resistant (MDR), extensively drug-resistant (XDR) and pan-drug-resistant (PDR) bacteria, increasingly common in South Africa.

Principi *et al.* (2016) establish that inappropriate antibiotic use causes the emergence of multi-drug resistance, which may lead to extended hospital admissions, augmented healthcare costs and amplified patient mortality. They also emphasise on related challenges, including cumulative incidence of *Clostridium difficile* Infection and the negative impression on microbiota. The under-treatment risk was also emphasised with under-dosing.

2.5.2.1 Children at high-risk of adverse effects of antimicrobial resistance

Even though the mortality rate of children under five in Africa (per 1,000 live births) declined from 163 in 1990 to 100 in 2011, the highest rates of child mortality still occur in Sub-Saharan Africa where one from nine children dies before the age of five, over 16 times the average for developed regions (one from 152) (UNICEF, 2012; Ester *et al.*, 2011). These rates are still insufficient to achieve MDG number four of the eight MDG's, stating that all 191-member states should reduce under five mortalities with 66% by 2015. The eight United Nations Millennium Development Goals (MDGs) form a blueprint, agreed by global countries and leading development institutions. They galvanised unprecedented efforts to meet the needs of the world's poorest by 2015 (Ester *et al.*, 2011). The revised MDG's (WHO, 2017) aim at reducing deaths by 2030, end preventable deaths of new-borns and children under five years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 live births and under-five mortalities to at least as low as 25 per 1000 live births (WHO, 2017).

The main causes of child mortality are well-known in the Sub-Saharan region, in order of importance: Neonatal causes (26%), child pneumonia (21%), malaria (18%), diarrhoea (16%), HIV/AIDS (6%), measles (5%) and accidents (2%) (Ester *et al.*, 2011). A recent WHO report reveals that pneumonia (13%), followed by diarrhoea (8%) are the leading infectious diseases, causing of death in children less than five years old, globally (WHO, 2016). The same sentiments were shared by the ESwatini statistics, where diarrhoea (8.1%) is the second leading cause of death, following pneumonia (15.2%) (UNICEF, 2016). In Sub-Saharan Africa,

pneumonia improved from 36% in 2000 to 46% in 2010 for rural areas and from 49% to 52% in urban areas (UNICEF, 2016).

ESwatini and South Africa hold the highest rate of mortality in children under five, associated with HIV (28% and 23%) respectively (UNICEF, 2012; WHO, 2011). In the World Health Statistics 2015 released by WHO, ESwatini failed to reduce the mortality rate of children under five during the period 1990 to 2013 (WHO, 2015). This represents a clear call for action for the country. Ester *et al.* (2015) allude that achieving the fourth MDG, which required reducing the mortality rate of children under five years old between 1990 and 2015, is evident that reaching these goals will require political participation, resources and suitable strategies at an innovative, exclusive level.

Gerber *et al.* (2010) establish that over 60% of hospitalised children received unnecessary antibiotics from 40 hospital in the United States over a one-year period. Principi *et al.* (2016) concur that overusing antibiotics is widespread in paediatrics and that numerous of these antibiotics are used inappropriately. Bowes *et al.* (2014) concur with Gerber *et al.* (2010), stating that it was reported (levy *et al.*, 2012; Pakyz *et al.*, 2009; Groskopf *et al.*, 2005) that an average percentage of 33%- 72% of hospitalised children receives at least one antibiotic in the United States, mostly for URTI's. Brink *et al.* (2016) agrees with Gerber *et al.* (2013) in that the majority (75 - 80%) of antibiotics for systemic use in adults and children are prescribed in the community, with acute respiratory tract infections (ARTIs) such as bronchitis, pharyngitis and sinusitis being the most common indications. The author further state that 60% of patients with an ARTI receive an unnecessary antibiotic, unlikely to be of benefit to their condition (Brink *et al.*, 2016). Collectively, this contributes to avoidable adverse events, stimulates the expansion of URTIs resulting in unnecessary costs (Gerber *et al.*, 2013).

Overusing antibiotics may elevate by diagnostic uncertainty (Llor & Bjerrum, 2014). The paediatric population can have viral infections and non-specific syndrome presentations and is therefore prone to inappropriate use of antibiotics, especially when the bacterial cultures are negative (Bowes *et al.*, 2014). At least two-third of infantile transience is correlated to infections and children are therefore possibly more susceptible than adults (Laxminarayan *et al.*, 2014). Mendelson *et al.* (2015) emphasised a report by Requejo, Newby & Bryce (2013) in a WHO meeting in Geneva. Access to antimicrobials and inhibition measures were important factors in reducing maternal and child deaths by half (50%) since 1990. Globally, after two decades, the number of

deaths of children younger than five years, still reached 7.6 million, regardless the increased access to antimicrobials, vaccination and other prevention measures against infectious diseases in countries encountering challenges in implementing maternal, neonatal and child health interventions (Mendelson *et al.*, 2015).

One from five emergency department visits in the US for adverse drug events in children younger than 18 years, are caused by antibiotics (CDC, 2017). Infections are still the main origin of neonatal deaths, even if effective antibiotics are available, which in turn account for over a third of the universal liability of child mortality (Laxminarayan *et al.*, 2014). The solution lies not only in the usage of existing knowledge to render antimicrobial resistance a national health priority, but also in the enactment of tailored containment strategies (Laxminarayan *et al.*, 2014). Attributable to the magnitude and the seriousness of the risks of bacterial infections in children, the study focussed on children younger than five years old.

Paediatric patients are at a higher risk of experiencing medication errors than adults because of the need for a dose calculation based on patient age, weight (mg/kg) or body surface area (mg/m²) and clinical condition (Aseeri, 2013). Kaushal *et al.* (2001) reported that medication errors with the potential to cause harm were three times more likely in children than in adult populations. These findings emphasise the importance of calculating the correct dose for the paediatric population, especially antibiotics.

Dosing medication to adults appears easy because recommended doses are determined in clinical trials involving adults, which is not the same with children (Anderson & Holford 2013). These proportion of the incorrectly doses used, are higher than the proportion (25%) reported by Storey *et al.* (2012). Miscalculation of paediatric dosing can lead to a tenfold or greater rate of dosing errors that can have harmful consequences for patients (Aseeri, 2013). Antibiotics and sedatives are the medications most extensively prescribed in the paediatric population and are the drug classes most reported, involved in paediatric medication errors (Aseeri, 2013). Kaushal *et al.* (2007) indicated that medication errors in paediatrics were observed in outpatients where the caregivers administered the medicine, it is suggested that they should be educated on the medicine administration to avoid preventable medication errors.

Regarding dosing of antibiotics in children, it must be considered, as for most medicines, the appropriate paediatric dose cannot be calculated simply from the adult dose using body weight as scaling factor (mg/kg).

This usually results in a dose too small for infants and children because elimination does not change in direct proportion to weight; a dose too large in neonates whose drug elimination pathways are immature (Anderson & Holford, 2013).

Regardless of the target dose, prescribers need a simple and rapid approach to identify the appropriate dose for each child (Bielicki *et al.*, 2015). Global guidance is inconsistent, with the US and much of continental Europe favouring exact weight-based dosing for pragmatic reasons. The UK applies age banded dosing with the WHO recommending weight banded dosing (Bielicki *et al.*, 2015). A simple and rapid approach will assist prescribers to select the correct doses. In developing countries, the prescriber is challenged by disease burden and a shortage of human and other resources.

Adherence to prescribed dosing recommendations, including dosing intervals, was listed as the most important modifiable factor that compromises treatment outcomes. Inadequate adherence to treatment recommendations was indicated to negatively impact patient outcomes (Bhoi *et al.*, 2017).

Lansky *et al.* (2007) assessed the consequences for antibiotic efficacy of various types of deficient adherence to a short-term dosing regimen. Four patterns of non-adherence were investigated: Dosage omission, irregular dosing intervals, delayed dosing and treatment discontinuation. Errors in timing of doses with a standard deviation less than two hours, had a minor effect on antibiotic efficacy, whereas dosage omission had a significant negative effect. Since non-adherence patterns are difficult to detect, recommended dosing regimens should be sufficiently robust against most doses (Lansky *et al.*, 2007).

Currently, children under the age of five, die from a lack of access to antibiotics for pneumonia, others die from antibiotic-resistant infections (Mendelson & Laxminarayan, 2016). Although more deaths can also be caused by resistance when antibiotics are too readily accessible, access to quality-assured antibiotics to all who need them is an ultimate human right, which was compromised in several regions. The innovative approaches of ASPs are designed to reverse the inequity of access versus excess (Mendelson & Laxminarayan, 2016).

2.5.3 Approaches and commitments for addressing antimicrobial resistance

It is recognised that global collaborative action is needed across all resource settings to confront the challenge of ABR (Cox *et al.*, 2017; UN 2017). Several LMICs are in the process of developing stewardship policies and programmes (Cox *et al.*, 2017), as countries endorsed their commitment to develop national action plans on AMR (UN, 2017). Policymakers realised that if left unattended, AMR will have significant social, health security and economic repercussions that will seriously undermine developing countries (UN, 2017). The critical function of national politicians in influencing laws that will enforce appropriate use of antibiotics to mitigate antibiotic resistance in developed and developing countries, was recognised (Laxminarayan *et al.*, 2012; Saam *et al.*, 2016). The challenge of AMR is that its impact cannot be easily quantified alike other conditions, such as HIV/AIDS and competing with other public health priorities (Laxminarayan *et al.*, 2012). More education and collaborative awareness-raising campaigns are required (WHO, 2015) by all affected sectors, including agriculture and environmental and natural resources sectors, ensuring appropriate regulations and standards will be legislated and facilitated effectively (WHO, 2015)

In ESwatini the burden of antimicrobial resistance is inadequately quantified; there is no comprehensive indication on the attributed mortality of resistance infections at a country level. This represents a crucial disadvantage, as it is difficult to prove the impact of antimicrobial resistance to policymakers, which is urgent but not as obvious as HIV/AIDS. Mendelson (2015) emphasises three fundamental pillars that need to be strengthened to combat ABR as follows:

“Firstly, through strengthened surveillance and reporting, as health care professionals and especially clinicians we should understand that the resistance profile of bacteria in our local environment or hospital is important as it ensures appropriate choice of an antibiotic that will be active against cultured bacteria” (Mendelson 2015, page:414). Secondly, “optimization of using the antibiotics to maximise its action (Antibiotic Stewardship) when a bacterium that requires treatment is identified or an empiric antibiotic(s) is needed before its identification” (Mendelson 2015, page: 415). Lastly, “we need to maximize infection control: prevent infection before it occurs by attending to social factors or drivers of infectious diseases, such as water supply and sanitation, and increase access to and coverage with vaccines” (Mendelson 2015, page 415).

The IDSA issued a policy statement titled “Combating Antimicrobial Resistance: Policy Recommendations to Save Lives,” provides clear suggestions for addressing the “synergistic crises” of increasing antimicrobial resistance and decreasing availability of new antimicrobial therapies (Barriere, 2014). South Africa took major steps in combatting antimicrobial resistance through its National Strategic Plan for AMR and implementing a clear plan for change (Mendelson, 2015). The National Strategic Plan includes national core standards for antimicrobial stewardship (and for infection prevention and control) that will be examined by the Office of Health Standards and Compliance. These standards include the requirement for stewardship committees and teams in all South African hospitals and at district level (Mendelson, 2015).

The WHO issued an endorsement for countries to develop an antimicrobial resistance containment strategic plan (WHO, 2015). ESwatini is drafting its National Strategic Plan on the containment of antimicrobial resistance in the country.

2.5.4 Developing ASPs

Mendelson *et al.* (2015) discussed the advantages and disadvantages of access, and excess to antibiotics. Principles and measures to promote rational antimicrobial use, are required to improve access to quality-assured antimicrobials, health services, prevention measures, diagnostics (preferably at the point-of-care), prescribing guidelines and education (Mendelson *et al.*, 2015). They allude that an integrated approach is needed to confront antimicrobial resistance, ensuring appropriate antimicrobial use, especially against bacterial infections (Mendelson *et al.*, 2015).

The IDSA, the Society for Healthcare Epidemiology of America (SHEA) and the Paediatric Infectious Disease Society (PIDS) define antibiotic stewardship as coordinated interferences intended to improve and measure the appropriate use of antibiotics by promoting selecting the optimal drug regimen (Barlam *et al.*, 2016). Ho *et al.* (2006) clearly articulate antibiotic stewardship as “the optimal selection, dosage and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance”. Strategies that improve antibiotic use are essential to combat microbial threat (Ho *et al.*, 2006).

The National Action Plan for containing antibiotic-resistant bacteria delivered in the White House in March 2015, recognised the need for antibiotic stewardship across all fields of healthcare (WHO, 2015). The antibiotic stewardship interventions aim at various players: Prescribers, patients, drug providers, policymakers and the public (Cox *et al.*, 2017). Institutions and hospitals recognised the inappropriate use of antibiotics and various countries developed action plans (Goff *et al.*, 2017). Most countries in the first world realised the importance of antibiotic stewardship (Goff *et al.*, 2017). Evidence indicates the effectiveness of antibiotic stewardship interventions at hospital level, including reduced hospitalisation, shorter treatment duration without an increase in mortality, and a reduction in colonisation and infection with resistant bacteria (Cox *et al.*, 2017).

In South Africa, alike other countries, antibiotic stewardship programmes successfully reduced antibiotic consumption (Boyles *et al.*, 2017). The existing antibiotic stewardship infrastructure in South Africa has important limitations. First, formal stewardship programmes mainly target postgraduate clinicians in hospital settings and have not reached outpatient and community settings, where most antibiotic prescribing occur (Boyles *et al.*, 2016). Secondly, programmes are usually led by infectious diseases physicians, who are a scarce resource in South Africa and unavailable in healthcare settings. Effecting sustained behavioural change concerning antibiotic prescriptions, requires an insight into and an appreciation of the factors leading to ABR (Boyles *et al.*, 2016).

The IDSA considers preauthorisation or prospective audit and reaction interventions as a robust strategy with moderate evidence in rendering ASPs successful (Barlam *et al.*, 2016). The society recommends the optimisation of therapy in ASPs. It is alluded that any antibiotic stewardship intervention must be customised, based on local needs, prescriber behaviours, barriers and resources (Barlam *et al.*, 2016). Restricted formularies were also identified as a crucial strategy for effective ASPs (Busing, 2011). Establishing formulary restriction and approval systems that include restricting broad-spectrum and later generation antimicrobials to patients where the use is clinically justified, can be effective in optimising antimicrobial use in a hospital setting in Australian hospitals (Busing, 2011). Busing (2011) findings are consistent with a study by Po, Nguyen and Carling (2012), where a significant decrease in linezolid use was observed in the 16-month follow-up period after implementing restricted formulary.

Rahal *et al.* (1998) facilitated extensive restrictions on using Cephalosporins. A significant decrease in ceftazidime-resistant *Klebsiella* infections and colonisation was achieved one-year later (Rahal *et al.*, 1998). Lewis *et al.* (2012) achieved comparable results where restriction of ciprofloxacin use led to increases in carbapenems use, associated with a significant decrease in the rate of resistance of *Pseudomonas aeruginosa* to ciprofloxacin and carbapenems. Restricting third-generation Cephalosporins antibiotics is recommended in ASPs as these are the force behind resistance in gram-negative bacteria (Paterson, 2006); their restriction is valuable in ASPs. Paterson (2006) indicates that a restriction of Ceftriaxone use in combination with ASPs result in increased efficiency and decreased duration of stay.

Barlam *et al.* (2006) conducted two surveys, directed to ASP directors and teaching and community hospitals. The goal “was to determine whether certain antibiotic stewardship interventions were universally instituted and accepted at top US academic centres and to document what interventions, if any, are used at both teaching and community hospitals within a geographic area” (Barlam & DiVall, 2006). They established that the hospitals instituted interventions to improve antibiotic prescribing, but none of the interventions were collectively accepted as essential or effective (Barlam & DiVall, 2006). Ninety-five per cent teaching hospitals had a restricted formulary, compared to 49% community hospitals; 89% teaching hospitals had an antibiotic approval process, compared to 29% community hospitals (Barlam & DiVall, 2006). ASP interventions therefore need to be customised rather than generalised.

Another intervention that was constructed to combat inappropriate use of antibiotics, is the conversion from intravenous (IV) to oral therapy (PO). Cyriac & James (2014) appraised the conversion from IV to PO, mentioning that short intravenous therapy for two to three days, followed by oral treatment for the remainder of the course, is beneficial to several patients. This is extensively practised in developing countries. Other previous studies have also commented on the positive influence of ASP on duration of hospital stay, readmission rate and mortality (Akpan *et al.*, 2015).

A prospective observational study accomplished for a period of six months in the Dr Pinnamaneni Siddhartha Institute of Medical Sciences and Research (Tejaswin *et al.*, 2018), indicated that only 43.68% of antibiotics were converted from IV-to-oral formulation. Duration of hospitalisation significantly ($p < 0.05$) decreased following IV-to-oral conversion of antibiotics in comparison with patients with non-conversion of antibiotics from IV-to-oral formulation (Tejaswin *et al.*, 2018).

Gums *et al.* (1999) describe shorter duration of hospital stays in the intervention group than the control group (9.0 vs. 5.7; $p = 0.0001$) and decreased mortality, namely 6.3% mortality in the intervention group compared to 12.0% in the control group. Ng *et al.* (2008), reported a noteworthy difference in duration of hospitalisation (7.46 and 6.97 respectively; $p < 0.001$) between the periods before and after ASP implementation with no difference in mortality.

Fischer *et al.* (2003) mention that several hospitalised patients continue to receive unnecessary prolonged intravenous medications. Another study by (Lee & Lindstrom, 2007) also emphasised that the major cost of managing community-acquired pneumonia (CAP) relates to the duration IV antibiotic use and duration of hospitalisation. They introduced guidelines on early switch to oral antibiotics and early discharge from hospital which may assist to achieve a unified approach to managing CAP (Lee & Lindstrom, 2007). Switching from IV to PO therapy as soon as patients are clinically stable can therefore reduce the duration of hospitalisation and lower associated costs without compromising clinical care (Fischer *et al.*, 2003; Tejaswini *et al.*, 2018; McLaughlin *et al.*, 2005).

Prescribing the recommended dose is important when prescribing antibiotics (Rello, 2007; Dryden *et al.*, 2011, Ghosh *et al.*, 2014 and Bielicki *et al.* 2015). Rello (2007) mentioned that optimal initial therapy comprises a broad-spectrum antibiotic, started in a punctual manner and administered at the correct dose and through the correct route. Ghosh *et al.* (2014) agree, mentioning that other contributing factors for emergence of resistance and treatment failure include, inappropriate use of antimicrobials concerning dose, frequency and duration, not considering compatibility and drug interaction effect of co-administered drugs.

Bielicki *et al.*, (2015) emphasise that correct antibiotic doses must be prescribed to achieve optimal bacteria disposal with minimal undesirable effects, such as drug toxicity or selecting resistant pathogens. Provided challenges associated with increasing antibiotic resistance, optimal use of antibiotics for children is important for global antimicrobial stewardship.

Some countries in Asia, including Singapore, Taiwan, Japan, South Korea and Thailand, have investigated methods to combat inappropriate use of antibiotics and documented challenges encountered with these strategies (Hsu *et al.*, 2012), including:

- Education programmes for the proper use of antimicrobials.
- Providing consultations from clinical microbiology or infectious disease specialists and trained pharmacists.
- Restriction of hospital formulary.
- Utilisation review based on guidelines and treatment algorithms for rational and appropriate usage.
- Monitoring and analysis of antimicrobial usage.
- Surveillance of antimicrobial susceptibility.
- Monitoring compliance to advise on choices of antimicrobial agents.
- Feedback to physicians.
- Conducting hospital infection control.

Exploring the most suitable approach for implementing an ASP is important as various interventions have a different influence, resulting in diverse patient outcomes (Barlam *et al.*, 2016). The primary goals of ASPs are improved clinical outcomes and reduced antimicrobial resistance (James *et al.*, 2012; Boyles *et al.*, 2013). There was immense inconsistency amongst the approaches towards overseeing antibiotic prescribing at hospitals and interventions for managing antibiotics were lacking (Allerberger & Mittermayer, 2008). It was concluded that further research was needed to define the best antibiotic stewardship approach for various hospital settings. Numerous authors (Dellit *et al.*, 2007; MacKenzie *et al.*, 2006; Madaras *et al.*, 2003; Struelens *et al.*, 2003; Ho *et al.*, 2006) emphasised the importance of formulating programmes to address AMR and the appropriate use of antibiotics, providing the best patient outcomes and reducing the risks of adverse effects. They emphasise the importance of formulating antibiotic stewardship guidelines. Barriere *et al.* (2014) insist that the onus of control of resistance is an ethical authoritative that is each person's responsibility.

The current practice in low resource countries is not conducive to combatting antibiotics resistance (Sprenger, 2017) and antibiotics are prescribed when it may not be beneficial to patients without directing therapy to the anticipated pathogens and often not using the suitable drug, dosage and duration (Bell, 2001; Knobler, 2003). At an individual patient level, an ultimate question needs to be directed before any antibiotic is prescribed, "Does this patient have a bacterial infection that requires an antibiotic?" (Mendelson 2015; page 415). Most often this question is relevant to primary care prescribers where inappropriate use of antibiotics was observed for viral URTI's, it applies equally to febrile patients admitted to hospitals at all levels

(Mendelson, 2015). The aforementioned author makes this statement, based on a study, exposing that patients are provided with up to 10 different antibiotics concurrently in both the private and public sectors in South Africa.

Ho *et al.* (2006) state that an ASP should not be observed as a programme to directly cut pharmaceutical and medical cost but should rather be observed as a strategy to enhance patient safety. He defined ASP as a multidisciplinary, programmatic, prospective, interventional approach to optimising using antimicrobial agents" (Ho *et al.*, 2006). Principi *et al.* (2016) agree with the definition provided by Ho *et al.* (2006), stating that multidisciplinary teams are considered essential to ensure adequate development of ASPs. The authors mentioned crucial members as drivers of an ASP, such as clinical microbiologists, infectious diseases specialists, infection control practitioners and clinical pharmacists. Several authors (Barlam *et al.*, 2016) recommended that commitment by hospital leadership and administrators, treating an ASP as a priority programme to improve and enhance antibiotic use, is essential to render it successful. The IDSA and SHEA strongly believe that ASPs are best led by infectious disease physicians with additional stewardship training, Barlam (2016).

In 2007, the IDSA published Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship, identifying paediatrics as a priority area for further research on the effectiveness of stewardship activities (Hersh *et al.*, 2015). The number of ASPs grew substantially in children's hospitals after the release of these guidelines (Hersh *et al.*, 2015). Studies indicate that paediatric ASPs signified favourable outcomes, including reductions in antibiotic prescribing and lower costs. A shortcoming identified, is the limitation of research to a small number of single-centred studies, instead of multi-centred studies (Hersh *et al.*, 2015).

Hersh *et al.* (2015) reported that after publication of the IDSA in 2007, antibiotic use decreased in the children hospitals, with a more pronounced change in those hospitals that established formal ASPs. Despite the growing evidence of the importance of ASP, several well-recognised obstacles hinder their growth and development. ASPs require substantial funding and education of prescribers (Principi *et al.*, 2016) and therefore, the development and the sustainability of ASPs are less likely in low resource hospitals. Prospective audits with feedback and previous approval of prescriptions belong to the core strategies for ASPs; these require dedicated personnel who may not be available in a paediatric setting with limited resources (Smith *et al.*, 2012).

Bowes *et al.* (2014) indicated that less than 20% of the staff held the appropriate knowledge on local resistance patterns for common bacteria. This evidence indicates that educational programmes are essential in ASP, but the challenge is that educational interventions require dedicated personnel and the educational material requires funding (Bowes *et al.*, 2014).

2.5.4.1 Antimicrobial stewardship programmes in the African context

Most studies on antibiotic stewardship were performed in high-income settings in Europe, the US and Australia (Cox *et al.*, 2017). A systematic review on the effectiveness of antibiotic stewardship in hospitals in LMICs is in preparation (Cox *et al.*, 2017). Limited studies provided data, identifying crucial interventional components and the effectiveness of ASPs in resource-limited settings (Brink *et al.*, 2017). A global survey of stewardship activities revealed that only 14% of respondents in Africa had an ASP established (Brink *et al.*, 2016). Several antimicrobial stewardship studies were conducted in South Africa (Boyles *et al.*, 2013; Mendelson, 2015; Mendelson, 2016; Brink *et al.*, 2016), but there is inadequate published information about the rest of the Southern African Development Community (SADC) region.

In South Africa, the South African Antibiotic Stewardship Programme (SAASP) was formed under the auspices of the Federation of Infectious Diseases Societies of Southern Africa (FIDSSA) (Mendelson, 2016). The SAASP comprises members from public and private sectors, comprehending the necessary skill sets of infectious disease physicians and paediatricians, veterinarians, microbiologists, infection and prevention control (IPC) practitioners, pharmacists, pharmacologists, intensivists, surgeons, epidemiologists and quality improvement experts (Mendelson, 2016).

2.5.4.2 Challenges of inappropriate antibiotic use, antibiotic resistance and barriers to antibiotic stewardship in weak health care systems

Antibiotics are essential in managing high-risk patients, including septic shock and other intensive care patients or those who are immunosuppressed (Mendelson, 2015; Mendelson, 2016). Although antimicrobial resistance is a natural occurrence, its spread is accelerated by misuse of antimicrobial medicine, deficient quality medicine, weak laboratory capacity and surveillance, insufficient regulation of using these medicines and inadequate or inexistent programmes for IPC (Mendelson 2015). Mortality is higher in antibiotic-resistant infections, as is morbidity and duration of hospitalisation (Cosgrove, 2006).

Antibiotic resistance causes a considerable financial burden in LMICs, because second- and third-line antibiotics will be required, and they are more expensive (Mendelson, 2015). Antibiotic stewardship is challenging in general and is even more so when human resources in the health care system, laboratory equipment, unavailability of drugs, limited or no policies exist or lack (WHO, 2015). It is difficult for governments to fund studies in LMICs, improving clinical outcomes (Laxminarayan *et al.*, 2014). In ESwatini, there are limited funds allocated for health research (MOH, 2017). This challenge extends attributable to the National Health Research office not recognised. Presently, members who review a protocol, do it voluntarily. The lack of research (Laxminarayan *et al.*, 2014), overuse and misuse of antibiotics, deficient sanitation, low vaccination rates and deficient infection control and practices (Cox *et al.*, 2017) lead to the misuse of antibiotics. Limited studies amongst several health care professionals, demonstrated the extent of the burden of inappropriate use and antimicrobial resistance in LMICs to convince policymakers of the urgent need to react emerging antimicrobial resistance (Laxminarayan *et al.*, 2014). In LMICs with weak health systems, the consequences of antibiotic resistance on health and economics are mainly undervalued and unstated (Laxminarayan *et al.*, 2014).

In South Africa, the main obstacles implementing ASPs in most public and private hospitals, were insufficient infectious diseases expertise and resources; additionally, in large hospital networks, the geographical distribution of these institutions also hindered implementation (Brink *et al.*, 2016). In the study by Brink *et al.* (2016) it was concluded that a multicentre antibiotic stewardship initiative, led by non-specialised pharmacists, decreased antibiotic prescribing across a large network of urban and rural hospitals in an infectious diseases resource-limited setting (Brink *et al.*, 2016). Messina *et al.* (2015) performed studies, indicating that ASPs led by non- infections disease experts, had impressive results. Messina *et al.* (2015), another pharmacist-compelled process enhancement intervention in the same hospitals, resulted in a significant change in the timing of administration (“hang time”) of intravenous antimicrobials in over 32 000 patients. ASPs centred on nurses, still have to be documented; the success of task-shifting ART management from doctors to nurses suggests that nurses could be an important addition to stewardship programmes within and external from South Africa (Boyles *et al.*, 2017).

2.5.4.3 Diagnostic challenges

Antimicrobial use contributes significantly to most hospital budgets; with 30 to 50% of patients receiving antibiotics in several circumstances in the US (Know *et al.*, 2003). The overuse of antibiotic is attributed by missed opportunities to reduce the burden of infections, especially in public hospitals (Laxminarayan *et al.*, 2012). Steps to reduce the burden of infections include the proper diagnosis of infections (Collins, 2005). In some situations, physicians might miss infections, because they have no access to diagnostic devices (Mendelson, 2015).

According to research published in 2017, childhood deaths occurred in Sub-Saharan Africa at the time (Feikin *et al.*, 2017). Most of these deaths are attributable to infectious diseases (Cox *et al.*, 2017; Feikin *et al.*, 2017). The burden of infectious diseases was significant in developing countries (Cox *et al.*, 2017). Countries with high rates of HIV (Cox *et al.*, 2017), malnutrition (UNICEF, 2007; Cox *et al.*, 2017) and malaria (Cox *et al.*, 2017) may render patients more susceptible to invasive bacterial infections.

Although there is evidence that there is a burden of infection in developing countries, the availability of clinical microbiology laboratories is limited in hospitals (Cox *et al.*, 2017). Currently, in South Africa, it is impossible to identify patterns of community compared to hospital-acquired bacterial resistance, attributable to a lack of linkage between laboratory and clinical data systems (Mendelson *et al.*, 2016). In Sub-Saharan Africa there are several deaths, attributable to infections not quantified, attributable to the absence of laboratory confirmations (Feikin *et al.*, 2017). The relevance of clinical bacteriology laboratories in low resource settings is increasingly documented as the increase in antimicrobial resistance is recognised as alarming (Barbe *et al.*, 2017)

Accurate, reliable and punctual laboratory testing is important for confirming clinical diagnoses, conducting precise infectious disease surveillance and directing public health care policy (Feikin *et al.*, 2017). An assessment of medical laboratories in Sub-Saharan Africa performed 10 years ago, revealed a system failure with unreliable analyses, leading to compromised patient care, unnecessary expenditures and a lack of trust from clinicians and health authorities (Barbe *et al.*, 2017). This dysfunctional system was declared a barrier to healthcare in Africa (Barbe *et al.*, 2017).

In developing countries, the laboratory and health care infrastructures are sometimes inadequate to meet the countries' needs, attributable to limited funds (Feikin *et al.*, 2017). The AMR crisis casts a new urgency on the need to improve performance levels as reference laboratories in Sub-Saharan Africa revealed severe shortcomings in bacterial identification and antimicrobial susceptibility (Barbe *et al.*, 2017). Limited access to reliable diagnostic testing, misdiagnosis occurs, resulting in inadequate treatment, increased mortality and an inability to determine the true prevalence of diseases (Feikin *et al.*, 2017). Inadequate access to laboratory testing led to clinicians finding alternative means of diagnosing disease, which causes uncertainty (Feikin *et al.*, 2017). As an example, it was indicated that access to rapid tests for diagnosing malaria in Zambia led to a four-fold reduction in inappropriate antimalarial prescribing and a five-fold increase in the appropriate use of antibiotics for pneumonia (Mendelson, 2015).

Barriers to laboratory testing in Sub-Saharan Africa are protean, are unique between and within countries and extend beyond economic constraints (Feikin *et al.*, 2017). Health care policymakers and clinical investigators need to promote rational, cost-effective diagnostic methods for infectious disease, with an emphasis on improvement (Feikin *et al.*, 2017). Although the life-threatening need for diagnosis of bacterial infections is recognised, clinical bacteriology only recently achieved eminence with policymakers, prompted by the increasing recognition of the looming crisis of AMR (Barbe *et al.*, 2017).

The World Health Organisation Regional Office for Africa (WHO AFRO) launched the Stepwise Laboratory Quality Improvement Process Towards Accreditation (SLIPTA) programme, which prepared clinical laboratories for ISO 15189 accreditation and also developed the Strengthening Laboratory Management Towards Accreditation (SLMTA) toolkit to support implementing SLIPTA (Barbe *et al.*, 2017). These measures introduced by WHO AFRO, yielded reliable results. There was an increase in accredited laboratories in the past years through the WHO AFRO initiative in producing quality laboratories in low resource settings (Barbe *et al.*, 2017).

2.5.4.4 Knowledge and awareness of healthcare professionals on antimicrobial use and resistance

Behaviour change is a main factor in correcting deficient prescribing practice (Mendelson, 2015). Inappropriate prescribing is compelled by a complex set of prescriber and patient behaviours (Mendelson 2015). In the WHO (2015) report, in a survey conducted in the six regions and 133-member states, revealed

that public awareness of antimicrobial resistance was generally low in all regions. This challenge was also observed in countries where national public awareness campaigns had been conducted (WHO, 2015). The low level of awareness on antimicrobial resistance was observed in sectors of health care, politics, the media and academia. ABR became an established threat to global health and inappropriate prescribing behaviours by clinicians, were identified as a major contributing factor (Boyles *et al.*, 2017). At community level, prescribing is often influenced by prescribers perceiving that their patients will be dissatisfied should they not receive an antibiotic, particularly for ARIs (Mendelson, 2015).

Inappropriate use of antibiotics contributes to several factors, including doctors' lack of knowledge, inexperience and a lack of health care professionals' education (Ghadeer, 2012). Ghadeer (2012) quoted earlier studies, indicating inappropriate prescribing and dispensing patterns, caused by prescribers and dispensers. Inadequate studies explicitly assessed paediatric prescribers' knowledge and clinical approach to scenarios illustrating contemporary principles of antimicrobial stewardship (Bowes *et al.*, 2014).

Containment of antimicrobial resistance requires changes in the antimicrobial prescribing behaviour of changes in antimicrobial prescribing patterns, (Abera, Kibret & Mulu, 2014). He emphasised that changes in antimicrobial prescribing patterns will demand changes in prescribers' behaviour towards the magnitude of the AMR challenge. He also emphasised that information on prescribers and nurses' knowledge and belief on AMR will permit developing more effective interventions on containment of AMR.

Ling *et al.* (2011), Mohamed *et al.* (2014), Barakh *et al.* (2016) conducted studies on public perspective on knowledge and attitude towards antibiotics, which partake a dynamic function in the achievement of treatment development. Results indicate that the public holds inadequate knowledge on antibiotics use and resistance.

2.5.4.5 Health care facilities

Health care facilities in LMIC's have are significantly challenged with a basic lack of infrastructure, large patient numbers and shortage of health care personnel with high turnovers and deficient job satisfaction (Cox *et al.*, 2017). Gaede and Versteeg (2011) agree with Cox *et al.* (2017) where they conclude that South Africa has deficient health outcomes, especially in rural areas, despite spending significantly more on health

than other middle-income and developing countries that produce advanced outcomes. A review of the state of health in SA, established insufficient progress in combatting HIV AIDS and malaria, no progress in improving maternal health and a deterioration in the mortality of children less than five years of age (Gaede & Versteeg, 2011).

2.5.4.6 Adherence to clinical practise guidelines

Clinical guidelines aim at assisting prescribers to render appropriate decisions concerning treatments for specific clinical conditions, comprising systematically developed reports (Principi *et al.*, 2016). For these guidelines to be effective, they need to be shared with all health care professionals involved in prescribing antibiotics, including infectious disease specialists, microbiologists and pharmacists (Principi *et al.*, 2016). Evidence-based clinical guidelines are also emphasised as an important device in promoting rational medicine use. They provide a benchmark of satisfactory diagnosis and treatment against which comparison of actual treatments can be made (WHO, 2002).

Rebbeck *et al.* (2013) allude to the importance of implementation approaches for clinical guidelines and indicated modest effects in changing health professionals' knowledge and practice. Targeted implementations are recommended as they suggest achieving proficient improvements. It was established that the patients attending training and later measured their compliance, significantly indicated a knowledge increase and were more likely to comply with the guidelines at follow-up (compliant at baseline 58%, follow-up 79%, $p = 0.002$) (Rebbeck *et al.*, 2013). It was concluded that a targeted implementation strategy improved health professionals' knowledge and clinical practice, enabling them more compliant with clinical guidelines. The importance of developing and implementing facility-specific clinical practice guidelines is also recommended. The two associations recommend using the clinical guidelines where feasible (IDSA 2007; SHEA 2012).

Barth *et al.* (2016) discuss the main barriers for clinicians to adhere to CPG, based on a review of adherence to clinical guidelines. The main factors were firstly identified as a lack of awareness, familiarity and agreement with the contents. Secondly, clinicians must sense that they have the skills to deliver on the CPG, able to overcome the inertia of "normal practice" and understand the need for change. Thirdly, the goals of clinicians and patients are not always the same. "Finally, there are a multitude of external barriers including

equipment, space, educational materials, time, staff, and financial resource” (Barth *et al.*, 2016, p.1133). In the UK, inadequate physician adherence to clinical practice guidelines was indicated, leading to deficient medical care quality (New England Healthcare Institute, 2008).

Ellodrt *et al.* (1995) determined factors that may led physicians not to comply with clinical practice guidelines in a large community teaching hospital. A retrospective analysis of patients whose physicians were not compliant with discharge recommendations from a prospective, controlled interventional trial of a guideline to reduce hospitalisation duration for patients admitted for chest pain (Ellodrt *et al.*, 1995). Physician refusal accounts for a small percentage (16%) of non-compliance. Implementation issues, such as health care system inefficiency and severity of illness were the predominant reasons why physicians did not comply with guidelines. The study further supported the principle that clinical practice guidelines should complement rather than be a substitute for physician judgement (Ellodrt *et al.*, 1995).

Gould (1999) identifies a need for hospitals to develop guidelines to combat the increasing bacterial resistance and to promote the adequate use of antibiotics. Smith *et al.* (2012) share the same sentiments, establishing that there were no adverse events associated with implementing the developed guidelines. Oh *et al.* (2011) indicate that adherence to guidelines for managing CAP, increased patients’ clinical outcomes. Even though the need for developing guidelines is identified, Halm *et al.* (2000) and Van De Beek *et al.* (2002) emphasised the challenge of low to moderate adherence to guidelines. Grol (1997) postulates that, for guideline implementation to improve, the magnitude to which prescribers observe the necessity for a guideline and support implementing that specific guideline before the guidelines are developed and facilitated, must be recognised.

Peter *et al.* (2004) conclude that a comprehensive enactment approach is required for prescribers to render their prescribing practices consistent with guideline recommendations. According to Peter *et al.* (2004), the reasons for barriers in appropriate use of antibiotics, using the prescribing practice guidelines, are as follows: A lack of dissemination of guidelines, uncertainty about the credibility of the content, an attitude that there is no need for guidelines, a lack of autonomy, insufficient knowledge, overestimation of the feasibility of an intervention and social and institutional context. The reasons for not implementing guidelines, varied extensively (Almatar, 2015). He acknowledged that several obstacles affect prescribers’ adherence, including the influence of senior doctors, were crucial in the non-compliance of guidelines, lack of awareness, the

requirement to do a calculation to assess the severity of the disease, existence of other conflicting guidelines and not expected to follow the guidelines.

CHAPTER 3: RESEARCH DESIGN AND METHODOLOGY

3.1 Study design and setting

3.1.1 Design

This was a single-centre process improvement study with a pre-intervention phase. During this phase, a baseline was established. This was followed by a preparatory period. Thereafter a multifaceted intervention, aimed at achieving the primary objective of the study, was facilitated to achieve the establishment and evaluation of an ASP, aimed at combatting the inappropriate use of antibiotics and managing AGE in children < five years of age. The term *intervention phase* is used to represent the period following the intervention.

The secondary objective, indicating investigating the KAP of healthcare professionals on antibiotics use and antibiotics resistance, was addressed by assessing the KAP of healthcare professionals involved in managing acute gastroenteritis in children before and after the intervention phase. The methodology for the primary objective is discussed first, followed by the methodology for the secondary objective.

3.1.2 Setting

The study was conducted at the RFM Hospital, one of the four high volume tertiary hospitals in ESwatini. The RFM Hospital is a 350-bed regional referral and teaching hospital situated in Manzini, the capital of ESwatini. The hospital occupies approximately 7,000 square metres of clinic buildings and 2,300 square metres of support buildings. The hospital is in the centre of ESwatini and is located in the most populated region.

3.1.3 Duration

The total duration of the study was 18 months. The research related to developing the ASP and its associated interventions, commenced with a six-month pre-intervention phase. Baseline data were collected between September 2015 and March 2016. This was followed by a preparatory period of six months. This period included developing the relevant clinical guidelines, developing the ASP terms of reference and research

training at the Tygerberg Hospital. This was followed by a six-month intervention phase, which occurred between September 2016 and March 2017.

Investigating the KAP of healthcare professionals working at the RFM, was conducted between September 2016 and March 2017, with an assessment before the intervention phase and another assessment at the conclusion of the phase.

3.2 Ethics approval

The Health Research Ethics Committee (HREC) at the Stellenbosch University (Ethics Reference number: S16/02/026) and the National Health Research Review Board (NHRRB) in ESwatini approved the study. RFM Hospital granted permission to conduct the study.

The primary objective did not involve any invasive procedures. The interventions introduced, created a standard of care in the hospital, therefore a waiver was obtained from the Ethics Committees (HREC and NHRRB) not to require informed consent by the children's guardians. Data was anonymously collected from patient records; study numbers were allocated, and no patient identifiers were collected.

A structured questionnaire (Annexure 2) was used for the secondary objectives. The participants were provided information on the purpose of the study, using the questionnaires to collect data, and the benefits of being part of the study; the participants were requested to sign an informed consent form (Annexure 3) if they were interested. Participants were assured that they had the right to decide to be part of the study with no repercussions.

3.3 Methodology for the primary objective: Developing and implementing an antibiotic stewardship programme

3.3.1 Study population

The following inclusion and exclusion criteria were used to define the patient population included in the pre-intervention phase and the intervention phase.

3.3.1.1 *Inclusion criteria*

The medical charts of children younger than five years of age, presented with AGE as a diagnosis during the six-month period of each phase, were included in the study. The following inclusion criteria were used:

- Children younger than five years of age.
- Children diagnosed with AGE as their primary diagnosis.
- For inclusion in the intervention phase, children had to be admitted within 24 hours of presenting and being diagnosed with AGE.
- For inclusion in the intervention phase, children had to be prescribed an antibiotic.

3.3.1.2 *Exclusion criteria*

Medical charts of children that met any of the following exclusion criteria, were excluded from the study:

- Children who were severely dehydrated, attributable to an underlying disease that could affect the assessment of hydration.
- Children with underlying chronic diseases, such as malignancy, gastroesophageal reflux, renal failure and liver disease.

3.3.2 **Collection of baseline data**

3.3.2.1 *Selection of cases for inclusion*

To identify cases of AGE for establishing baseline data for the pre-intervention phase, the entries in the admission book in the children's ward of all patients who were admitted between September 2015 and March 2016, were reviewed. All patients who were admitted with any form of diarrhoea during this period, were selected. This strategy was based on experience gained from a previous study, conducted at the same hospital, to assess the management and treatment of children less than five years, presented with diarrhoea in 2013 (Matsebula-Myeni, 2013). These include cases of wrong diagnoses by doctors. To anonymise patient data, anonymous participant codes were assigned to each case, identified from the list of admissions.

3.3.2.2 *Data extraction*

A structured data extraction form (Annexure 4) was used to collect relevant demographic and clinical features from the medical charts for each patient. This would establish a baseline against which the interventions could be evaluated. Basic demographic data, including age, gender and source of diarrhoea (community vs hospital-acquired diarrhoea) were captured in the data extraction form. Extracted data included comorbidities, names and duration of the antibiotic used, total duration of stay (hospital days) and drug allergy history. Clinical notes by the prescribers in the daily rounds, were perused and interpreted with prescribers' assistance.

During the pre-intervention phase, there were no antibiotics prescribing guidelines, antibiotics prescription forms and restricted antibiotics prescription forms; these sections of the antibiotic stewardship form were therefore not completed. Chemistry tests were available before the intervention phase. Cultures (stool and blood) were not routinely performed in the laboratory; the sections on cultures could not be completed on the data extraction device for all cases.

During the pre-intervention phase, there were no ward rounds where the laboratory technician and the research were involved. Prescribers made therapeutic decisions or alterations without involving other healthcare professionals; there were no documented recommendations from other healthcare professionals. Decisions to continue with a certain therapy or the addition of other laboratory investigations, depended solely upon the ward doctor. From the review of the files, follow-up on laboratory results and the availability of required medication from the Pharmacy, appeared inadequate.

3.3.2.3 *Review of baseline data*

The baseline data was reviewed to identify issues in managing AGE in children < five years of age. The issues and concerns identified during this review were used to inform the preparation of the multifaceted intervention to address the identified inappropriate managing AGE management.

3.3.3 Training at Stellenbosch University and Tygerberg Academic Hospital

In preparation for the study, one month was spent at Stellenbosch University and the Tygerberg Academic Hospital for training. The hospital pharmacist at Tygerberg Academic Hospital were consulted and all documents used by the hospital concerning the ASP and managing acute gastroenteritis, were reviewed. The purpose of the training was to expose the research to the ASP established at the hospital and to be familiarised with materials used during ward rounds. During this training, the research was exposed to the prescriptions that were sent to the Pharmacy, indicating the antibiotic prescribing form, the restricted antibiotics prescribing form and the contributions by the pharmacist before dispensing the medication. The research conducted observed the ward rounds by the paediatrician in the gastro-enterology ward. Access to the clinical guidelines (AGE guidelines, hydration guidelines and antibiotic prescribing guidelines) was allowed. These were used in the paediatrics' ward and processes followed by nurses in taking patient history and managing patients in the ward, were observed.

3.3.4 Preparatory activities for antibiotic stewardship programme implementation

3.3.4.1 Establishment of an antibiotic stewardship committee

The research developed the terms of reference (TOR) of the antibiotic stewardship committee (ASC) (Annexure 5). The Senior Medical Officer at RFM Hospital approved the TOR. Members of the ASC were then appointed and tasked with establishing an ASP. The members of the ASC were identified, based on their individual expertise and included a pharmacist (the researcher), a paediatrician or the ward doctor and a laboratory technician (Annexure 5). Core members of the ASC were tasked to perform ward rounds concurrently, according to their functions indicated in the TOR, daily between Monday and Friday for the six-months intervention period. The ASC core objectives are described in Annexure 5.

3.3.4.2 Establishment of a steering committee

A steering committee was established, comprising the members of the paediatrics department. The paediatrics department comprised a paediatrician, general practitioners and family nurse practitioners. The steering committee was responsible for developing the relevant clinical practice guidelines (Section 3.3.5).

The recommendation of the National Institute for Health and Care Excellence informed the rationale for the composition of the steering committee (NICE, 2014). When developing guidelines, it is crucial to involve the individuals who might be affected by the guideline recommendations in a collaborative and transparent way. The practitioners managing childhood diseases, were the stakeholders involved in developing and implementing the guidelines. Their function was to contribute to the draft initial guidelines developed according to their relevant expertise. Their contribution ensured that the guidelines addressed issues relevant to them and met patients' health needs. It was ensured that the guidelines included medicines readily available in the hospital, procured with ease when required. The microbiologists ensured that all the laboratory tests that could be requested during the intervention, were in order.

3.3.4.3 Development of prescription forms

The steering committee reviewed the new prescription forms, adopted from Tygerberg Hospital. The forms were as follows:

- Antibiotic prescribing form (Annexure 6).
- Restricted antibiotic prescribing form (Annexure 7).

Seven antibiotics were restricted in treating AGE and its comorbidities in the hospital. These included: Ceftriaxone, which was previously established to be inappropriately used in children diagnosed with AGE (Matsebula-Myeni, 2014) Ciprofloxacin, which is not indicated for children under 12 years or with a body weight, less than 40 kg; Piperacillin; Meropenem; Clindamycin; Tazobactam and Vancomycin; these five antibiotics are not included in the ESwatini national general patient's formulary, since they are reserved for ICU or renal hospital patients.

3.3.5 Development of clinical practice guidelines

The steering committee was responsible for developing the following clinical practice guidelines:

- Diagnosis, treatment and managing AGE and its comorbidities - namely pneumonia, bronchitis, pharyngitis, otitis media and tonsillitis (Annexure 9).

- Antibiotic prescribing guideline (Annexure 8).
- SAM guideline (Annexure 10).

Guidelines that were developed by the Tygerberg Academic Hospital in Stellenbosch (an antibiotic prescribing guideline and an acute gastroenteritis guideline accompanied by a hydration protocol) were used as a basis for developing an empirical clinical practice treatment guideline for common AGE comorbidities for the RFM Hospital. The practice guidelines that were used at Tygerberg Academic Hospital were modified. The prescribers at the RFM Hospital were consulted through the steering committee, regarding the modification of the guidelines to encourage the latter to 'own' the guidelines and fully facilitate them. The steering committee discussed these guidelines at the RFM Hospital during weekly meetings held every Tuesday from February 2016 to April 2016. The head of the paediatrics' department chaired the meetings, coordinated through the research. All comments and feedback were documented, and relevant issues were discussed with the research supervisors at the Tygerberg Academic Hospital and the paediatrician at Tygerberg Hospital.

These guidelines were developed primarily to achieve the best patient outcomes, with a secondary aim to encourage prescribers' adherence to the guidelines. Multidisciplinary teams from the RFM Hospital, which included the Antibiotic ASC and the hospital guidelines and policy team, consulted Tygerberg Academic Hospital. These teams included critical care doctors, a surgical specialist, paediatricians, pharmacists, a microbiologist and nurses. The main goal was to involve specialists or departments, involved in treating patients in the children's ward. Although the study did not include children with surgical conditions, all children at RFM Hospital use the same ward but children are admitted in various cubicles. It was also considered advantageous for all prescribers to be aware of the standard of care being introduced in the hospital.

The Ministry of Health (MOH) disseminated a SAM guideline document in use at RFM during the study. The existing MOH guideline was compared with the SAM guideline from Tygerberg Hospital. The two guidelines agreed but the Tygerberg guideline was easier to read and follow. The research collaborated with the steering committee, facilitating the Tygerberg Academic Hospital guideline document.

3.3.6 Implementing the antibiotic stewardship programme and associated interventions

Before implementing the ASP, the study was explained to all the children's ward staff, which included the sisters in charge, staff nurses and nursing assistants, ensuring that they understood the new procedures established during the intervention study period.

3.3.6.1 Implementing clinical practice guidelines

Printed copies of the clinical practice guideline were distributed in the children's outpatient department, emergency department, laboratory department, special care unit department and the Pharmacy department. During the intervention phase, implementing the newly established clinical guideline was assessed, including the acute gastroenteritis guideline (accompanied by the hydration protocol), the antibiotic prescribing guideline and the SAM guideline. The hydration protocol included six checklist questions and the antibiotic prescribing guideline, and the SAM guideline included 10 checklist questions each. Each guideline data extraction form had a compliant and a non-compliant field or section at the end. A prescription was considered compliant when it comprised over five correct responses in the AGE or hydration protocol section, and over eight correct responses in the antibiotic prescribing guideline and the SAM guideline.

3.3.6.2 Identification of cases for inclusion in the antibiotic stewardship programme

The ASP was facilitated in the 2nd week of September 2016 by the following process. The researcher identified medical charts of eligible participants each morning before the ward round. Patients who met the inclusion criteria, none of the exclusion criteria and who had received antibiotics for less than 24 hours were eligible to be included in the ASP. Medical records were reviewed prospectively by the research in the ASP team, with the assistance of the ward doctor and the nursing sister in charge (where necessary).

3.3.6.3 Accompanied ward rounds

The main activity of the antibiotic stewardship programme was the accompanied ward rounds as per the TOR (Annexure 5) of the ASC members. These ward rounds commenced in the second week of September 2016, when the ward doctor could be accompanied during each ward round. A dedicated laboratory technician,

assigned to the microbiology bench in the laboratory, was expected to be present. The department was short staffed; therefore, the research was discussed with the laboratory technician. Any information that needed his attention after the ward round was discussed with him. He could also be called in during the ward round. During the intervention phase, the children's ward was visited every morning between Monday and Friday to see if there were any AGE admissions. All patients diagnosed with AGE's files were retrieved from the filing cabin in the children's ward.

The ward round comprised a review of clinical notes and the results of laboratory and X-ray investigations. These were collected and analysed to establish the indication, planned duration and appropriateness of antibiotic therapy. Depending on each patient's case, the cases were followed up as needed. Patients with severe acute malnutrition were followed up daily, as SAM with diarrhoea have high fatality rates.

All relevant information needed, were followed up from the medical charts, contained in the data extraction form. Before the physical ward round, the following aspects were checked:

- The diagnosis matched the clinical presentation of the patient.
- The hydration guideline on admission was followed.
- The presence of any diagnosed comorbidities.
- Adherence to the antibiotic prescribing guideline.

A course of antibiotic therapy was considered inappropriate and was eligible for ASP enrolment, if any of the following criteria were met:

- Inappropriate dosage, defined as errors in dosage (under-dosing and over-dosing), frequency or formulations of antibiotics based on dose ranges suggested by the South African Medicine Formulary (SAMF), considering specific conditions, such as renal or liver dysfunction.
- Antibiotic-bacteria mismatching (bacteria/drug mismatching), defined as use of a requested or current antibiotic with suboptimal activity against the bacteria according to culture or susceptibility results.
- Inappropriate antibiotic selection for documented infection, which included susceptibility to a narrower-spectrum agent, such as use of a gram-positive antibiotic for a gram-negative bacillus. The definition of inappropriate selection also included inappropriate route of administration, such as use of intravenous

therapy if the oral form of therapy was considered acceptable (guideline followed to determine acceptability, Annexure 8).

- Inappropriate spectrum of coverage, which included therapeutic duplication (double coverage). This involves the prescription of two or more antibiotics with the same antibiotic activity, which is unnecessary (such as Piperacillin/Tazobactam and Metronidazole for treating anaerobic infections).
- Inappropriate indication, indicating no evidence of infection or the infection was a viral infection for which antibiotics were unnecessary. There was absence of clinical, laboratory or radiographic evidence of infection or the presence of documented or suspected viral infection.
- Contraindication based on the patient's drug allergy history, defined as the prescription of an antibiotic to patients with known allergies to a particular antibiotic or antibiotic class.
- Prolonged duration of therapy, defined as unnecessarily prolonged therapy for the indicated infection based upon standards established by the SAMF.

Patients who needed immediate attention were discussed with the ward doctor, including:

- Severely dehydrated patients.
- Patients with SAM.
- Patients with SAM accompanied by severe dehydration.
- Patients with SAM and kidney function tests that indicated infection.
- Patients who had no or pending chemistry results but were initially diagnosed with moderate to severe dehydration.

Each case was reviewed by the ward doctor and laboratory technician, considering local resistance patterns and then decided if the antibiotic use was appropriate. Decisions regarding inappropriateness, reasons why the use was inappropriate and recommendations for changes in antibiotic use, were collected on the standardised data extraction form (Annexure 4).

Patients admitted on weekends or holidays were not enrolled in the ASP, unless enrolled in the study less than 24 hours after the start of antibiotic use; patients admitted after 12:00 pm on Sunday were enrolled in the study as the ward rounds are conducted between 08:00 am and 12:00 pm each weekday. The prescriber who admitted the patient, was contacted telephonically or a physical meeting was arranged in cases where

there was inappropriate management of the diagnosed disease and if a lack of correction could cause a serious adverse reaction. These cases included the following instances:

- Patients who were eligible for bolus infusion, who did not receive it.
- Patients who received wrong intravenous fluids by bolus administration.
- Patients who received wrong maintenance intravenous fluids.
- Patients who received a higher dose of antibiotics with ambiguous chemistry results.
- Patients who were severely dehydrated and prescribed gentamycin without kidney function tests.
- Patients showing impaired renal function.

Prescriber's on-call between 5:00 pm and 8:00 am were eligible to order restricted antibiotics without approval. In such cases, prescribers were not allowed to order over three doses without the restricted order form. During ward rounds, the ASC core members discussed cases where restricted drugs were used and decided whether to continue with the antibiotic. Use of restricted antibiotics was approved up to a specified 'stop date', but the research was allowed to dispense the restricted antibiotics after this date to prevent lapses in dosing for critically ill patients. The prescribing doctor or the laboratory was consulted for the relevant results. Once the information was collected and a prolonged treatment required, the patient could continue to receive the antibiotics until the treating doctor decided on a discontinuation. Resubmission of requests for restricted antibiotics before the approval stop date was encouraged.

3.3.6.4 Recommendations

Following the assessment of using all antibiotics and restricted antibiotics, all recommendations were recorded in the structured data extraction form. A change in using antibiotics or other related recommendations were suggested; the final decisions regarding antibiotic choices were left to the ward doctor, who was a member of the ASP team, or to the paediatrician. Documented recommendations were the following:

- Discontinue antibiotics: elimination of duplicate therapy or unnecessary therapy.

- Modifying therapy: Adding an antibiotic, prescribing an antibiotic with a narrower or broadened spectrum, adjusting antibiotic dose or duration, changing the route of administration, or recommending an alternative therapy because of patient allergy.
- Specialist consultations: When the antibiotic choice was complex, attributable to the complicated nature of the patient's condition and a specialist consultation was considered necessary.
- Other recommendations: Monitoring laboratory parameters, recommending sterile site cultures, removal of an infected source (the removal of a potentially infected device, for example, the intravenous cannulas).

The recommendations were deliberated with the ASC, documented and kept in the relevant patient's file. In the absence of an infectious disease specialist at the RFM Hospital, cases of complex diseases or treatments were referred to the paediatrician. For each patient, more than one type of recommendation could be recorded; in this instance, all recommendations were captured on the data extraction form.

The research conductor and the ward doctor were responsible for discharging patients. Thereafter, complicated cases were discussed in the following regular ASC meeting, including:

- Severe dehydration with SAM.
- Re-admissions of SAM with dehydration and oedema.

3.3.6.5 Control of restricted antibiotic use

Use of restricted antibiotics required prior approval by the research, with close supervision by the paediatrician, especially in complicated cases (Annexure 7).

3.3.6.6 Laboratory investigations

The Laboratory Standard Operation Procedure (SOP) was adopted and the following tests were performed during the intervention.

3.3.6.7 *Plasma glucose test*

Finger prick plasma glucose tests were performed in every child admitted with moderate to severe dehydration before the child was sent to the ward (Annexure 11).

3.3.6.8 *Liver and kidney function tests*

All patients with moderate to severe dehydration were tested for U&E before hydration with the appropriate intravenous fluids. For patients who presented with malnutrition as a comorbidity, kidney function tests were performed. The COBAS INTEGRA 400 PLUS test was used to analyse blood, cerebrospinal fluid (CSF) and urine chemistry estimations. A volume of 4 ml of blood was collected for the testing of all chemistry parameters in a Serum Separator Tube (SST) (yellow top) or plain container (red top). Each sample tube was labelled with the sample identification (ID) and Patient identification (PTID) number. The calibration, quality control, results processing and reporting and chemistry reference ranges are detailed in Annexure 14.

3.3.6.9 *Stool culture*

Fresh stool samples were collected on admission or during admission from patients to whom antibiotics were prescribed, preferably before administration of the antibiotics. The stool specimens were collected in a screw-capped sterile container and transported to the laboratory within two hours of collection.

Upon reception at the laboratory, the specimens were provided unique bar codes for identification and then sent to the microbiology department for analysis. The stool specimens were macroscopically examined before culture and then inoculated onto Xylose Lysine Deoxycholate (XLD) agar, Sorbitol MacConkey, MacConkey and Salmonella Shigella Agar by spreading a pea sized portion of the stool on the culture plate using an applicator stick. An inoculating wire loop was then used to streak the stool with flaming in between streaking to obtain single colonies. Selenite broth was also used for enriching the stool specimens. A pea sized portion of the stool was inoculated into selenite broth using an applicator stick. The plates and broth were incubated at 37 °C aerobically for 16-24 hours after which the plates were observed for growth. The selenite broth was sub-cultured onto XLD and incubated for a further 16-24 hours at 37 °C.

All plates with growth were observed for colonial morphology and distinct features on each media used. Gram staining was accomplished to classify the bacterial isolates and further identification of the organisms with biochemical tests was conducted. The biochemical tests conducted included indole test, Kligler iron agar, motility, urease production and oxidase and citrate utilisation test (Annexure12)

3.3.6.10 *Antibiotic sensitivity testing*

Antibiotic sensitivity testing was conducted using the Kirby-Bauer disc diffusion method. An inoculum of the test organism was prepared by adding 3 to 5 colonies into 3 ml of normal saline. The turbidity of the inoculum was adjusted to match 0.5 McFarland standard solution. The inoculum was streaked onto Mueller Hinton agar using the lawn streaking technique. Antibiotics were then seeded onto the streaked plates within 10 minutes. The plates were incubated at 37 °C for 18 hours after which they were checked for antibiotic sensitivity (Annexure 13)

3.3.6.11 *Radiographic investigations*

X-ray investigations were performed in patients with comorbidities like bronchitis and pneumonia or with SAM. The severe acute gastroenteritis guideline required that both the chest X-ray-AP and lateral were taken in each patient. The chest X-rays were read and interpreted by the doctor.

3.3.7 Collection of intervention data

The structured data extraction form (Annexure 4) was used to collect the relevant demographic and clinical features from the medical charts for each patient to compare any improvement in managing AGE when interventions for appropriate managing AGE were put in-place. The data extraction form was completed using data from medical charts and discussions made during the ward rounds. Basic demographic data including age, gender and source of diarrhoea (community vs hospital-acquired diarrhoea) were captured in the data extraction form. Clinical and other data included comorbidities, name and duration of the antibiotic used, total duration hospitalisation (hospital days) and history of drug allergy were also collected. The recommendations made during the ward rounds were recorded.

3.3.8 Measures of effectiveness of the antibiotic stewardship programme

The following measures were used to assess the effectiveness of the ASP.

- Days of therapy (DOS).
- Cost of antibiotic therapy.
- Duration of hospitalisation.
- Targeted antibiotics consumption.
- Appropriateness of antibiotic therapy.
- Patient outcomes.

3.3.8.1 *Days of therapy*

The days of therapy (DOT) for each patient, were measured. The DOT was recorded for each antibiotic administered, regardless the dose and the frequency. For example, a patient who received amoxicillin 250mg, eight-hourly for three days had three DOT, whereas a patient receiving both amoxicillin 250mg, eight-hourly for three days and Metronidazole 100mg, eight-hourly for three days would have six DOT.

3.3.8.2 *Cost of antibiotic therapy*

The cost of antibiotic therapy was determined from the cost of each dose of the antibiotic used, obtained from the electronic system of the hospital Pharmacy and the duration of treatment.

3.3.8.3 *Duration of hospitalisation*

The duration of hospitalisation was calculated for each patient. The number of hospitalisation days were calculated from the time the patient was admitted.

3.3.8.4 *Targeted antibiotic consumption*

The proportion of restricted antibiotic versus unrestricted antibiotics used in the study were recorded. The restricted antibiotics were the targeted antibiotics, monitored in the study.

3.3.8.5 Proportion of inappropriate antibiotic courses and compliance with ASP team recommendations

The proportions of antibiotic courses that were inappropriate and needed review by the ASP team were determined on admission and the rate of compliance with ASP team recommendations were determined during the ward rounds or on Day 3 by examining patients' medical records to determine whether: (i) the antibiotic course was still inappropriate; and (ii) the ward doctor had accepted the ASP team's recommendation. The compliance rate was defined as the proportion of all changes made by the ward doctor/ nurses in compliance with the ASP recommendations (treatment providers made changes after the communication with the ASP team in the intervention group) divided by all recommendations recorded in the data collection form by the ASP team.

3.3.8.6 Antibiotic stewardship programme team recommendation at variance with culture results

For cases in which alternative therapy (broadened or narrowed empirically) was recommended, it was determined whether any of recommended therapies were inconsistent with the antibiotic susceptibilities of any cultured organisms.

3.3.9 Measures of patient outcomes

3.3.9.1 Development of subsequent infection

For cases in which it was recommended to stop therapy, it was determined whether the patients developed subsequent laboratory-confirmed infections, or any infections defined by the ward doctor. Patients who were discharged were followed up to see if they developed a subsequent infection (suspected nosocomial infection) within 72 hours following the ASP recommendation to discontinue antibiotic therapy. A nosocomial infection can be suspected in cases occurring within 48 hours of hospital admission, three DOS discharge or 30 DOS an operation (Revelas, 2012).

3.3.9.2 Readmission for AGE

The researcher identified patients who were re-admitted for AGE within a week after discharge.

3.3.9.3 *Mortality*

Patients who died, had cause of death recorded. Mortality was calculated as number of deaths/ total number of patients enrolled in the study.

3.4 Methodology for secondary objective: Investigation of the knowledge, attitude and practices of health care professionals on antibiotic use and antibiotic resistance

3.4.1 Study population

The following inclusion and exclusion criteria were used to define the participants population included in the pre-intervention phase and the intervention phase.

3.4.1.1 Inclusion criteria

- Healthcare professionals including doctors, pharmacists, Pharmacy technicians and laboratory technologists, who were managing children admitted at the children's ward
- Agreement to participate in the study.

3.4.1.2 Exclusion criteria

Healthcare workers that were not considered technical for the study; phlebologists, Pharmacy assistants and nursing assistants.

3.4.2 Procedure

To increase awareness and facilitate developing educational programmes and strategies for the appropriate use of antibiotics by the health care professionals working at the RFM Hospital, their KAP related to antibiotic use and antibiotic resistance was assessed. A quantitative research method was followed using a survey instrument developed for this purpose. To determine whether the ASP and its associated interventions resulted in any changes in the KAP of healthcare professionals the assessment was conducted at two time

points. The first assessment was performed before the intervention phase of the study and the second at the end of the intervention phase. A non-experimental, descriptive-correlational research design was used for the assessment.

3.4.3 Survey instrument

3.4.3.1 Development and validation of the KAP questionnaire

A literature review was conducted of studies with performed similar surveys. The survey instrument was developed based on two studies by Awad *et al.* (2015) and Thriemmer *et al.* (2013). The original questionnaire of Awad *et al.* (2015) focussed on the knowledge, attitudes and practices towards antibiotic use amongst the public in Kuwait. The second study by Thriemmer *et al.* (2013) investigated the knowledge, attitudes and practices amongst medical doctors and students in the Democratic Republic of Congo. A pilot study was conducted by four various healthcare professionals from the target participants. The participants in the pilot study were not included in the study. The questionnaire was then modified by the research, using feedback received from the professionals. To test the reliability of the instrument, a pilot test of the survey instrument was conducted using two modes of data collection (paper and electronic). The questionnaire was distributed to 30 individuals with a medicine or health sciences background.

Revisions of the KAP questionnaire was made based on feedback from the pilot and included re-wording, re-ordering and removal of some questions.

3.4.3.2 Structure and content of the survey instrument

The final version of the questionnaire (Annexure 2) comprised four sections that addressed the aims of the secondary objective. The four sections are described below.

- Section A: Demographic profile of the healthcare professionals

Demographic questions were included at the beginning of the questionnaire to establish the characteristics of the participants. As the purpose of the secondary objective was to investigate the perspectives of

healthcare professionals, the first demographic question sought to define the sample by asking participants to mention their professional background. Additional demographic questions sought to identify the highest level of education of each participant, the number of years since graduation, gender and age. The participant's professional background was particularly important to address the research questions and provide a basis for comparison between variables.

- **Sections B to D: KAP of the health care professionals**

Section B comprised 27 questions that assessed the knowledge of the health care professionals. Section C comprised nine questions on attitudes. Section D comprised 12 questions related to behaviour.

All the sections used a five-point Likert scale (Strongly Agree, Agree, Neutral, Disagree and Strongly Disagree) designed to capture the knowledge, attitudes and practices of healthcare professionals using scaled responses. A Likert scale is a rating scale in which the attitude of the respondent is measured on a continuum from one extreme to another with an equal number of positive and negative response possibilities and one middle or neutral category (Rea & Parker, 2005). As a framework for data analysis and presentation, five health care dimensions were developed:

- Antibiotic resistance.
- Antibiotic use.
- Antibiotics misuse.
- Healthcare professionals' beliefs.
- Health care practices.

Each dimension comprised a response scale and the health care professionals were asked to indicate their perceptions across the five dimensions. The following conceptual definitions and number of items for the five health care dimensions were used:

- Antibiotic Resistance: Health care professional's knowledge and beliefs regarding antibiotic resistance.
- Antibiotic Use: Knowledge and beliefs regarding antibiotic use.
- Antibiotics misuse: Healthcare professionals' knowledge and perception of antibiotics misuse.

- HCP's beliefs: HCP's beliefs pertaining to antibiotic use and antibiotic resistance.
- Health care professionals Practices: Practices by HCPs regarding antibiotic use and antibiotic resistance.

3.4.4 Recruitment

Healthcare professionals were approached during their meetings and provided information on the study. They also had an opportunity read the information leaflet and to ask questions where they were not clear. Informed written and signed consent was obtained from participants who voluntarily agreed to participate in the study. The participants were not provided any incentive for participating in the survey.

3.4.5 Conduct of the survey

Paper-based, self-administered structured questionnaires were distributed to staff members who had provided informed consent to participate in the KAP assessment. The informed consent forms were signed before the participants completed the questionnaire. The participants completed the questionnaire in the meeting room and submitted the completed questionnaire to the research. The participants completed the questionnaires without any use of reference material. During completion of the questionnaire, the researcher was available for providing clarifications on any of the questions if necessary. The researcher captured the data provided by the participants and submitted the raw data to the statistician.

The pre-intervention KAP survey was conducted between the 3rd and the 7th of September 2016. The post-intervention survey was conducted between the 20th and the 24th of March 2017. Nurses who were unavailable during the day shift, who were on night shift were missed in this exercise

3.5 Statistical method

3.5.1 Sample size and power calculation

For the evaluation of the primary objective a sample size of 200 patients, 100 in each arm, was used. The sample size was calculated as follows:

A study conducted in 2014 by Huttner *et al.* (2014), demonstrated a 10% to 25% decrease in antibiotic use. In a study conducted by Cairns *et al.* (2013), total broad-spectrum antibiotic use decreased immediately by 16.6% ($p < 0.001$) when the intervention commenced in the ICU. The assumption was made that the intervention would reduce the number of children for whom antibiotics were incorrectly prescribed by 15%, with 80% power and a significance level set at 0.05, leading to a required sample size of 200, with 100 in the pre-intervention and 100 in the post-intervention phases.

There are approximately 1500 admissions of children between 0 to 12 years presenting with all conditions annually in the children's ward at RFM Hospital. The hospitalisation records for the period of January 2012 and December 2012 were retrieved and the following information was derived: 80% of the 1500 admitted children were between 0 - five years; meaning that an average of 1200 children between the ages of 0 - five years were admitted per year. Of these approximately 240 children (20%) had AGE as the main diagnosis. If this number is halved, it means that in six months 120 children presented with and were admitted for AGE. It was estimated that it would be possible to identify approximately 120 children for inclusion in the study during each of the 6-month periods of the pre-intervention and intervention phases. The researcher identified 87 cases for inclusion in the pre-intervention phase and 126 for the intervention phase (sections 3.3.2.1 and 3.3.6.2 above). The realised sample was slightly different from the calculated sample size, with less than the 100 required cases identified in the pre-intervention and more identified in the post-intervention phase. There was enough power to achieve the primary objective, as described later in the results section.

3.5.2 Statistical analysis

The analysis was conducted using STATA software version 14 (Stata corporation, 2016), as described below. P-values below 0.05 were used for statistical significance and 95% CIs reported for estimates were appropriate.

3.5.2.1 Analysis for the primary objective

The Shapiro-Wilk test was performed to test measured data for normal distribution. Normally distributed measured variables were presented as means and standard deviations; whilst medians and interquartile

ranges (IQR) were described for non-normally distributed data. Frequencies and percentages were calculated to describe basic demographic and clinical data in the pre-intervention and intervention groups for categorical variables. Student's t-test for continuous variables (or Wilcoxon sum rank test, if data were not normally distributed) and Pearson's chi-squared test for categorical variables were used to determine whether there were significant demographic or clinical differences between pre-intervention and during intervention use of antibiotics, proportion of antibiotics used and compliance to ASP recommendations. If a categorical variable had a cell with fewer than five cases, Fisher's exact test was performed for normally distributed variables.

To understand using antibiotics, DOT per 100 patient-days, cost of antibiotic therapy and duration of hospitalisation for the six months of the pre-intervention phase were compared with those for the six months of the intervention phase. Causative agents (from stool samples) and sensitivity patterns (from blood samples) of the bacteria were analysed and presented as frequencies. Proportions of inappropriately prescribed antibiotics i.e. the incorrect antibiotic was prescribed for the causative agent, were also reported. The chi-square test was used to determine statistically significant differences in antibiotic prescribing, managing acute malnutrition and appropriate hydration between the pre-intervention and intervention phases.

3.5.2.2 Analysis for the secondary objective

For the comparison of the KAPs of various groups of healthcare professionals (doctors, pharmacists, Pharmacy technicians, nurses and laboratory technologists) at the RFM Hospital, the knowledge, attitudes and practices were summarised as scores and expressed as percentages. A knowledge score above or equal to 80% was considered as good knowledge, attitude and practice and a score below 80% considered as deficient knowledge, attitude and practice. The Kruskal Wallis test was used to compare KAP scores between various groups of healthcare professionals; and a chi-squared test was used to compare the good or deficient knowledge, attitudes and practices categories in the questionnaire. Additional analyses tested the association between demographic variables (professional background, level of education, age, gender and years of experience) and KAP scores.

CHAPTER 4: RESULTS

4.1 Introduction

This chapter outlines the results of both the pre-intervention and the post-intervention phase of the study. The results related to implementing the antibiotic stewardship programme (and the associated interventions) are presented first, followed by the results for investigating the KAP of healthcare workers.

4.2 Results: Antibiotic Stewardship programme and associated interventions

4.2.1 Demographic and clinical data of the patients

There were 150 admissions that were initially identified and coded in this way. Of these, 30 cases were subsequently identified as deaths, four as re-admissions (one patient was re-admitted twice and two patients were each re-admitted once; the initial admission and re-admissions were consolidated as a single case for each patient, thus three cases in total), four cases of chronic diarrhoea and seven cases of bloody diarrhoea. The remaining 106 admissions were confirmed as cases with AGE as primary diagnosis. When the research went to the chart room to retrieve the patient files only 94 files could be located although the electronic system identified their physical location. Of the 94 files retrieved, two files were of patients with bloody diarrhoea and information was missing from five of the patient files. The total number of patient files available for review was therefore 87.

In the six months after implementing the intervention, 153 patients were admitted with AGE. Of these, 18 patients were excluded from the study as they had been admitted more than 48 hours before. Three patients passed away before being enrolled into the study, four patients had bloody diarrhoea and two patients had chronic diarrhoea. A total number of 126 patients were therefore identified for inclusion in the intervention phase.

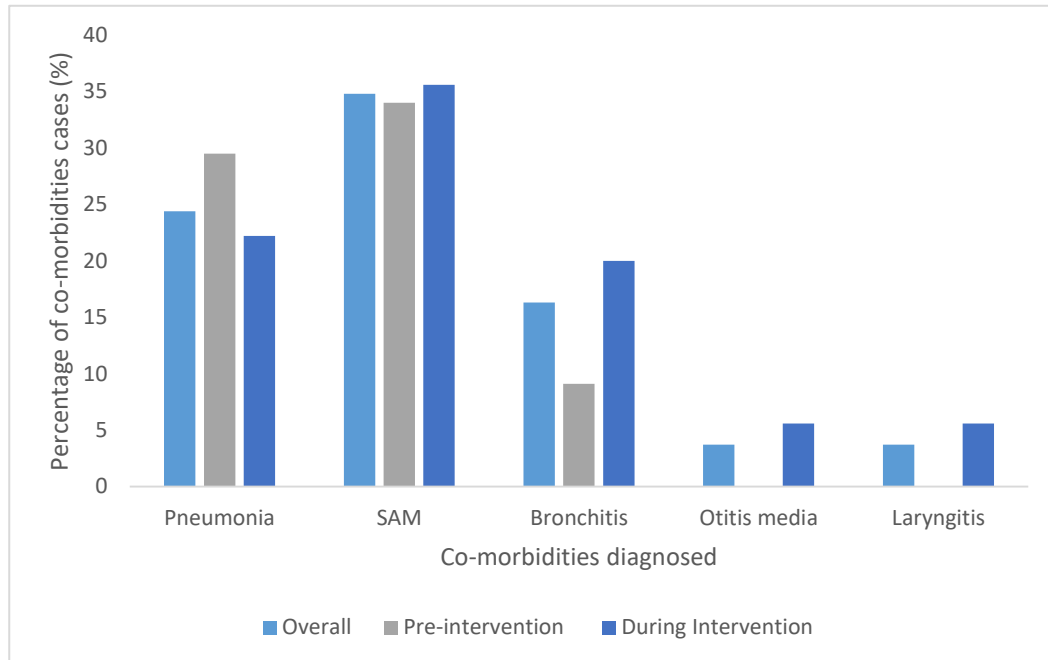
The demographic characteristics of the patients were the similar in the pre-intervention and intervention phases of the study (Table 4.1). The median age of patients included in the study was 10 months, with an

interquartile range of 5-15 months. The median age of patients whose files were included for collecting baseline data during the pre-intervention phase was 9 (5-14) months whereas the median age (IQ range) of children included study during the intervention phase was 10 (5-15) months, (Table 4.1). The difference between the median ages for the two phases was not statistically significant ($P= 0.4882$). Most the patients were male in both phases of the study and there was no statistically significant difference in gender.

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS	UNITS	OVERALL, N= 213	PRE-INTERVENTION (N = 87)	DURING INTERVENTION (N = 126)	P-VALUE
AGE MEDIAN (IQR) N=213	Months	10(5-15)	9(5-14)	10(5-15)	0.4882
GENDER N(%), N=212	Females	101(47.9)	42(48.8)	59(47.2)	0.815
	Males	110 (52.1)	44 (51.2)	66 (52.8)	
WEIGHT, MEDIAN (IQR), N=213	Kg	7.3 (5.8-9)	7(5.2-8.5)	7.43(6-9)	0.1064
BODY TEMPERATURE, MEDIAN (IQR) N=213	°C	37.9 (37.9-38.7)	38 (37.2-39)	37.8(36.7-38.5)	0.170

Table 4.1: Demographics and clinical characteristics of children included in the study

Figure 4.1: Comorbidities diagnosed in all patients and during the pre-intervention phase and during the intervention phase separately



Malnutrition was the most common comorbidity observed in the two phases of the study, followed by pneumonia and bronchitis (Figure 4.1). In the intervention phase, the number of pneumonia cases was lower, and the number of bronchitis cases was higher than in the pre-intervention phase. A few patients were diagnosed with otitis media and laryngitis during intervention phase. There were rare cases, 2 (1.58%), where patients had more than one comorbidity. Of the 140 patients who were diagnosed with comorbidities in the study, 47 (34.8%) had severe acute malnutrition as one of the comorbidities, the percentages were almost the same in the pre-intervention and post-intervention (Figure 4.1).

4.2.2 Effectiveness of the antimicrobial stewardship programme

Of the 126 patients who were included in the intervention phase, 70 patients presented with cases that were eligible for ASP review. These were patients who needed modification of their antibiotics therapy. The antibiotics measures that decreased in the intervention phase were the antibiotics used, restricted antibiotics used, duration of therapy, DOT and the cost of antibiotics used. A statistically significant difference was

observed in the restricted antibiotics used ($P < 0.001$), DOT ($P = 0.003$) and the cost of antibiotics used ($P = 0.0024$).

4.2.2.1 Targeted antibiotic consumption

- **Antibiotic use**

All patients who were admitted for AGE and its comorbidities received antibiotics. The number of antibiotics used per patient remained at two in both phases of the study. There was no statistically significant difference observed in the antibiotic use between the two phases of the study.

- **Restricted antibiotic use**

From the total of 212 patients who received antibiotics in the study, there were 124 patients who received restricted antibiotics, including 69 patients (79.31%) in the pre-intervention phase and 55 patients (43.65%) in the intervention phase respectively. This difference was statistically significant ($P < 0.001$).

- **Days of therapy and duration of hospitalisation**

A statistically significant difference was observed in the duration of therapy and duration of hospitalisation between the two phases of the study, with $P = 0.0003$ and $P = 0.001$ respectively (Table 4.2).

ANTIBIOTICS MEASURE VARIABLES	UNIT	OVERALL	PRE- INTERVENTION	DURING INTERVENTION	P-VALUE
DURATION OF THERAPY, MEDIAN (IQR) N=213	Days	5(3-5)	5(5-5)	4(3-5)	0.0003
DURATION OF HOSPITAL STAY, MEDIAN (IQR) N=213		5(3-6)	5(5-7)	4(5-7)	0.0001

Table 4.2: Duration of antibiotic therapy and duration of hospitalisation during the pre-intervention and intervention phase

4.2.2.2 Cost of antibiotic therapy

The average cost of the antibiotics used per patient in the intervention phase was E43.40 (E27.00-E109.00) compared to the pre-intervention phase E81.50 (E54.50-E121.70). A statistically significant difference of $P=0.0024$ was observed.

4.2.2.3 Proportion of inappropriate antibiotic courses

A decline in the number of inappropriate antibiotic courses was observed in the intervention phase and a statistically significant difference was observed ($p<0.001$) for all the variables listed in Table 4.3, except for the recommended doses prescribed ($p=0.891$).

Variable		Overall (%) N=212	Pre-intervention (%) (N=87)	During intervention (%) (N=125)	P-value
Decision appropriate for prescribing an antibiotic on admission, n (%)	No	122(57.55)	65(74.71)	57(45.60)	<0.001
Appropriate empirical antibiotics prescribed before microbial testing, n (%)	No	124(58.49)	77(88.51)	47(37.60)	<0.001
Definite treatment prescribed after microbial testing, n (%)	No	106(72.60)	78(73.58)	28(26.42)	<0.001
Doses prescribed as recommended by the clinical practice guidelines, n (%)	No	35(16.43)	14(16.1)	21(16.8)	0.891
Doses administered at correct dosing interval during admission, n (%)	No	95(44.81)	53(60.92)	42(33.60)	<0.001

Table 4.3: Inappropriate antibiotics courses in the pre-intervention and during the Intervention

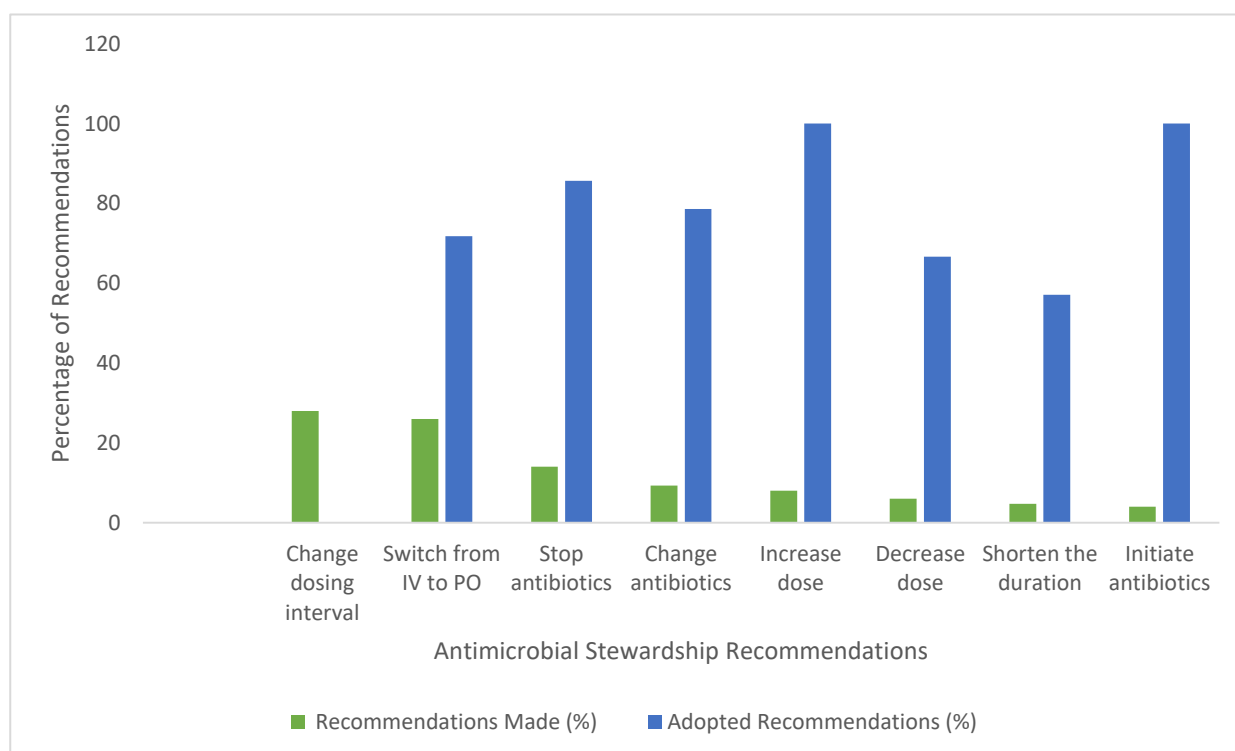
4.2.2.4 Antibiotic stewardship recommendations

There were 150 recommendations made by the ASP core team during the intervention phase. The recommendations most frequently made were “Change dosing interval”, “Convert from IV to oral” and “Stop antibiotics”. Two recommendations were adopted fully in all cases, i.e. “Increase dose” and “Initiate antibiotics”. Recommendations for changing the dosing interval were not adopted. The other recommendations were partially adopted (“Stop antibiotics”, “Change antibiotics” and “Decrease dose”).

- **Antibiotic stewardship recommendations adopted**

Out of the total of 150 recommendations made by the ASP core team during the intervention 85(56%) were adopted. “Increase of dose” and “Initiate antibiotics” were the fully adopted. None of the antibiotic stewardship recommendations of “Change dosing interval” were adopted.

Figure 4.2: Antimicrobial stewardship recommendations made and adopted during the intervention



- **Proportion of antibiotic stewardship recommendations at variance with culture results**

From the total of 150 recommendations made, 35 recommendations informed by culture results and sensitivity results, which were “Stop antibiotics” (21, 14%) and “Change antibiotics” (14, 9.33%). The proportion of recommendations proposed informed by culture results was 23% and the proportions of recommendations adopted at variance with culture was 17.1%

4.2.2.5 Patient outcomes

- **Development of subsequent infections**

There were no patients who developed subsequent infections during the intervention phase.

- **Re-admissions for AGE**

There were four cases of re-admissions in the pre-intervention phase compared to the intervention phase where one readmission was observed.

- **Mortality**

During the intervention phase two patients passed away within an hour of admission, before they were enrolled in the ASP and were excluded from the number of deaths observed during the intervention phase. There were 30 (22.1%) deaths observed in the pre-intervention phase compared to the 15(11.9%) deaths during the intervention phase. The causes of death during the pre-intervention phase were as follows: 14 deaths caused by SAM, seven deaths, attributable to AGE, four deaths, attributable to sepsis, pneumonia or bronchitis and five deaths, attributable to severe dehydration.

4.2.3 Bacterial cause of acute gastroenteritis

4.2.3.1 Culture results

No culture or antibiotic sensitivity tests were performed in the hospital during the pre-intervention phase. During the intervention phase, 59 laboratory requisition forms were completed by prescribers for stool culture, one for blood culture and one for CSF.

The positive cultures of organisms were divided into four groups, namely: Enteropathogenic *Escherichia coli* (*E. coli*), Gram- positive bacilli, gram-negative bacilli and *Klebsiella*. For Enteropathogenic *Escherichia coli* (*E. coli*) there were 20 positive cultures (32.79%) and two (3.28%) positive cultures were reported as gram-

positive bacilli, with no specific organism mentioned. There were also seven positive cultures (11.58%), which were reported as gram-negative bacilli, with no specific organism mentioned. There were two positive cultures (3.28%) of *Klebsiella*. Nineteen samples (31.15%) did not yield significant growth and 11 samples (18.03%) were not analysed by the laboratory department.

4.2.3.2 Sensitivity results

Drug sensitivity tests were performed for all samples that had positive cultures (31 cultured samples, 100%). *E.coli* was resistant to Ceftriaxone (13 samples), cotrimoxazole (5 samples), chloramphenicol (5 samples) and amoxicillin (8 samples). *E.coli* was sensitive to gentamycin (6 samples), nalidixic acid (9 samples) and ciprofloxacin (5 samples). Gram-positive bacilli (one cultured from blood) were resistant to Ceftriaxone (2 samples), Metronidazole (2 samples), gentamycin (1 sample), nalidixic acid (2 samples) and amoxicillin (2 samples). Gram-negative bacilli were resistant to Ceftriaxone (4 samples), cotrimoxazole (4 samples) and chloramphenicol (3 samples). Both *Klebsiella* samples tested were resistant to Ceftriaxone, gentamycin and cotrimoxazole, but sensitive to nalidixic acid.

4.2.4 Compliance with clinical practice guidelines

4.2.4.1 Antibiotics prescribing guideline

A statistical significance (<0.001) difference in antibiotic prescribing in the pre-intervention and during intervention was observed, except the doses prescribed variable, which indicated no statistical significance difference (0.891) between the two phases of the study (Table 4.4).

Variable		Pre-intervention, n (%)	During Intervention, n (%)	P-value
Decision appropriate for prescribing an antibiotic, n (%)	Yes	22(25.29)	68(54.40)	<0.001
	No	65(74.71)	57(45.60)	
Culture conducted before administration of antibiotics, n (%)	Yes	2(2.30)	35(28.00)	<0.001
	No	85(97.70)	90(72.00)	
Appropriate empirical antibiotics prescribed, n (%)	Yes	10(11.49)	78(62.40)	<0.001
	No	77(88.51)	47(37.60)	
Definite treatment prescribed after relevant assessment	Yes	5(12.5)	35(87.5)	<0.001
	No	78(73.58)	28(26.42)	
	Not applicable	4(4.60)	62(49.60)	
Practised infection control, n (%)	Yes	3(3.45)	100(80.00)	<0.001
	No	84(96.55)	25(20.00)	
Were antibiotics evaluated appropriately, n (%)	Yes	31(35.63)	110(88.00)	<0.001
	No	56(64.37)	15(12.00)	
Use of microbiology and other relevant tests for informing managing infection, n (%)	Yes	32(36.78)	73(58.40)	<0.001
	No	55(63.22)	46(36.80)	

Variable		Pre-intervention, n (%)	During Intervention, n (%)	P-value
	Not applicable	0(0.00)	6(4.80)	
Doses prescribed as recommended in clinical practice guidelines, n (%)	Yes	73(83.9)	102(81.6)	0.891
	No	14(16.1)	23(18.4)	
Switching from intravenous therapy to oral therapy, n (%)	Yes	5(5.75)	39(31.20)	<0.001
	No	80(91.90)	37(29.60)	
	Not applicable	2(2.35)	49(39.20)	
Doses administered at right correct dosing interval, n (%)	Yes	34(39.08)	81(64.80)	<0.001
	No	53(60.92)	42(33.60)	

Table 4.4: Statistically significant differences in antibiotic prescribing in the pre-intervention and during intervention

4.2.4.2 Guideline for the diagnosis, treatment and managing AGE and its co-morbidities

In the following sections, the guideline for the diagnosis, treatment and managing AGE and its comorbidities will be referred to as the *AGE guideline*.

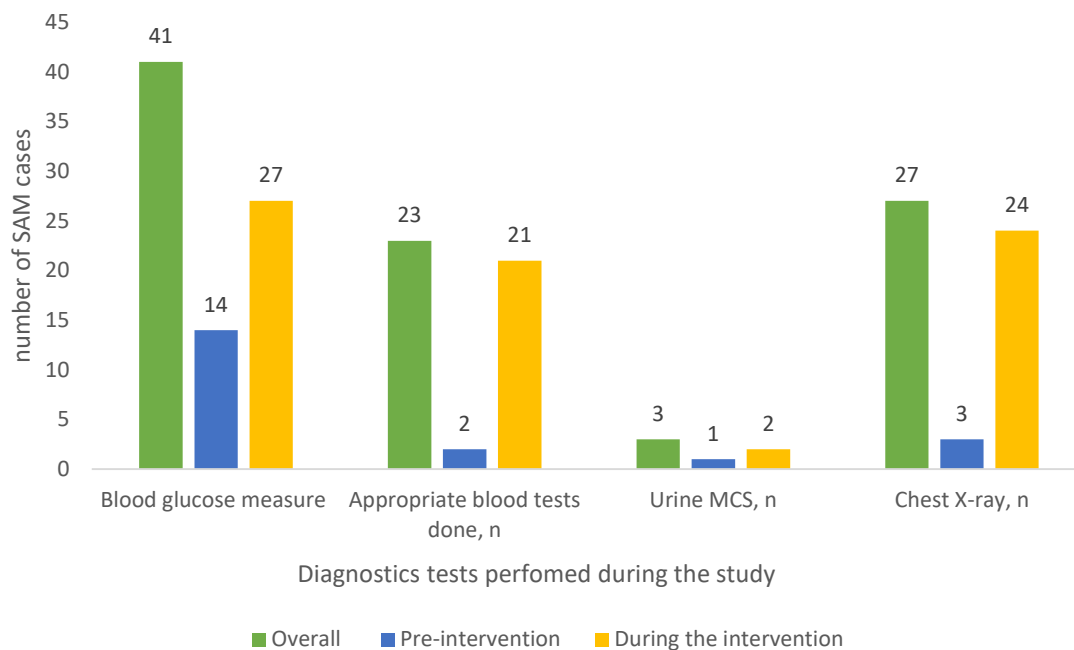
- **Severe acute malnutrition**

After an assessment of every child admitted for AGE at RFM Hospital during the study period, a total of 44 patients were diagnosed with SAM. In the pre-intervention phase, there were 17 patients diagnosed with SAM and 27 patients in the intervention phase. Improvements to the diagnostic measures required by SAM guideline for the proper diagnosis and managing SAM are indicated in Figure 4.3. There was a statistically significant difference in the number of appropriate diagnostic measures (plasma glucose measure, appropriate blood tests, urine Microscopy Culture and Sensitivity and chest X-ray) that were performed during the intervention phase compared to the pre-intervention phase ($p < 0.001$). Most (41/44) of the patients' urine was not cultured. Only one urine test was performed in the pre-intervention phase and only two urine tests were performed during the intervention.

Out of the total of 44 patients who were diagnosed with SAM in the study overall, 41 patients were checked for plasma glucose on admission. During the intervention phase, plasma glucose tests were performed for all 27 patients on admission and in the pre-intervention, only three patients were not checked for plasma glucose.

Most patients in the intervention phase (21/27) underwent appropriate blood tests (albumin, renal function test). In the pre-intervention phase only two of the 17 patients underwent appropriate blood tests. There was a statistically significant difference between the two phases of study ($P < 0.001$) for the performance of appropriate blood tests. In cases where the results indicated an infection, urine MCS (Microbiology, Culture & Sensitivity) was conducted and it was conducted for three patients in the study. In the pre-intervention phase, the urine MCS could not be performed as the albumin and renal tests were not performed in majority of the patients. During the intervention phase, eight patients were eligible for urine MCS but only two patients had urine cultures performed.

Figure 4.3: Number of patients (%) with severe acute malnutrition in whom appropriate diagnostic tests were performed during the pre-intervention phase



For the study, 39 of the patients were provided appropriate nutritional feeds, 14 patients in the pre-intervention phase and 25 patients in the intervention phase. The number of patients who were provided the appropriate fluids were higher in the intervention phase 19 patients, in comparison to the pre-intervention phase where nine patients were provided appropriate fluids, but the increase was not statistically significant ($P = 0.072$). Chest X-rays were performed in 27 patients diagnosed with SAM in the study overall, mainly to determine the presence of tuberculosis (TB) co-infection, amongst other possible infections. A statistically significant difference between the pre-intervention and the intervention phases was observed for the number of chest X-rays ($P < 0.001$). Most patients, namely 24 patients, had a chest X-ray taken in the intervention phase.

A total of 21 of 44 patients diagnosed with SAM were checked and their electrolytes corrected where needed and there was a statistically significant difference between the two phases of the study ($P < 0.001$). Twenty-four patients of the 27 patients diagnosed with SAM in the intervention phase were provided micronutrient supplements and three patients of the 17 patients were provided micronutrient supplements in the pre-

intervention phase. Out of the 44 patients admitted with SAM in the study overall, there were 30 patients who had an appropriate follow-up planned and most them (23 patients) were in the intervention phase.

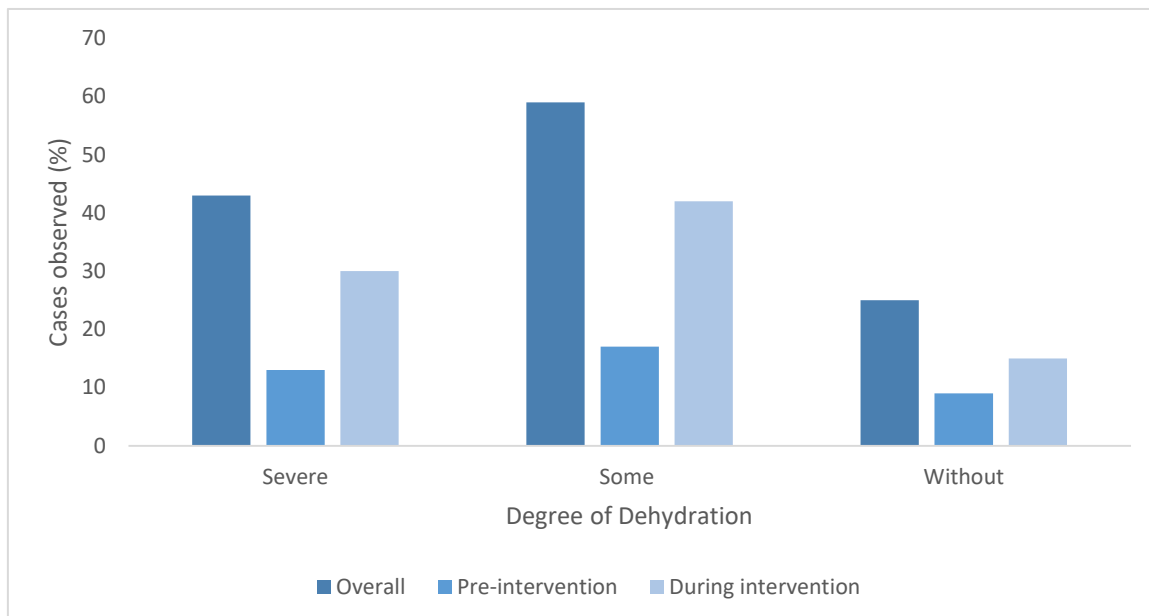
VARIABLE		OVERALL	PRE-INTERVENTION	DURING INTERVENTION	P-VALUE
NUTRITIONAL FEEDS, N	Yes	39	14	25	0.297
	No	5	3	2	
HYDRATION APPROPRIATE, N	Yes	28	9	19	0.072
	No	13	8	5	
	Not applicable	3	0	3	
ELECTROLYTES CORRECTED, N	Yes	21	1	20	<0.001
	No	23	16	7	
MICRONUTRIENTS SUPPLEMENTED, N	Yes	27	3	24	<0.001
	No	17	14	3	
FOLLOW-UP PLANNED APPROPRIATELY, N	Yes	30	9	21	0.002
	No	14	8	6	

Table 4.5: Statistically significant difference in treating severe acute malnutrition in the pre-intervention and during the intervention

- **Acute gastroenteritis guideline (Hydration protocol)**

There was a statistically significant difference ($P < 0.001$) between the pre-intervention phase (43.7%) and during the intervention phase (70.6%), in prescribers mentioning if there was dehydration or no dehydration accompanying the diarrhoea. Fifty-nine per cent of the patients had some dehydration, followed by those who were severely dehydrated (43%). A statistically significant difference between the two phases in the categorised degree of hydration was not indicated ($P = 0.734$).

Sixty-one patients in the study was eligible to receive rehydration through a short-term infusion, of these patients 46 (75.41%) received the rehydration through a short-term infusion and 15 (24.59%) did not receive through a short-term infusion. All the patients who received the rehydration through a short-term infusion was established in the intervention phase of the study. There was a statistically significant difference ($P < 0.001$) between the number of patients who received rehydration through a short-term infusion during the pre-intervention and intervention phases of the study.

Figure 4.4: Degree of dehydration observed in the pre-intervention and during the intervention

Most of the patients who received short-term infusion in the study, namely 45 (78.95%), received an appropriate fluid replacement. In 12 patients (21.05%) the type of intravenous fluid was not mentioned. There was a statistically significant difference in the appropriateness of the intravenous fluid used ($P < 0.001$) between the pre-intervention and intervention phases.

Most patients, namely 170 (79.81%) received appropriate fluid maintenance replacement in the study and a statistically significant difference between the pre-intervention and intervention phases ($P < 0.001$) was observed (Table 4.6). There was no statistically significant difference between the two phases in the correct rate and appropriate volume of rehydration fluid administered in the study. Most of the patients, namely 172 (80.75%) received fluids at a correct rate and the appropriate volume was used in the study (Table 4.6). There were 111 (52.86%) biochemical investigations (renal function tests and plasma glucose) that were conducted appropriately in the intervention phase, whilst 98 (77.78%) biochemical investigations were conducted in the pre-intervention phase (Table 4.6).

Appropriate routine medication (vitamin A and zinc sulphate) was provided to 161 patients (77.40%) in the study, whilst 34 patients (16.35%) were not provided the appropriate routine medication (Table 4.6) and a

statistically significant difference ($P < 0.001$) between the two phases was observed. Most of the patients in the intervention phase, namely 111 (88.10%), were provided the appropriate medication, compared to the pre-intervention phase, in which 50 (60.98%) were provided the appropriate medication (Table 4.6).

Variable		Overall, N (%)	Pre-intervention, N (%)	Intervention, N (%)	P- value
Appropriate fluid for bolus infusion, n (%)	Yes	45(78.95)	0(0.00)	45(78.95)	<0.001
	No	12(21.05)	0(0.00)	12(21.05)	
Method of rehydration appropriate, n (%)	Yes	166(77.93)	49(56.32)	117(92.85)	<0.001
	No	47(22.06)	38(43.68)	9(7.14)	
Appropriate fluid used, n (%)	Yes	170(79.81)	50(57.47)	120(95.24)	<0.001
	No	43(20.19)	37(42.53)	6(4.76)	
Correct rate and volume of fluid used, n (%)	Yes	172(80.75)	50(57.47)	122(96.83)	<0.001
	No	41(19.25)	37(42.53)	4(3.17)	
Investigations conducted appropriately, n (%)	Yes	111(52.86)	13(15.48)	98(77.78)	<0.001
	No	76(36.19)	69(82.14)	7(5.56)	
	Not applicable	23(10.95)	2(2.38)	21(16.67)	
Routine medication provided, n (%)	Yes	161(77.40)	50(60.98)	111(88.10)	<0.001
	No	34(16.35)	30(36.59)	4(3.17)	
	Not applicable	13(6.25)	2(2.44)	11(8.73)	

Table 4.6: Hydration management in acute gastroenteritis cases in the pre- intervention phase and during the intervention

4.3 Results: Knowledge, attitude and practices of health care professionals on antibiotics use and antibiotics resistance

4.3.1 Demographic characteristics of the participants

A statistically significant difference ($P < 0.001$) concerning the professional background of the participants during the pre-intervention and the intervention phases of the study was observed (Table 4.7). Gender and highest education level did not indicate any statistical significance difference ($P = 0.951$) and ($P = 0.207$) respectively.

A total of 34 healthcare professionals were recruited during the pre-intervention phase and included medical doctors (9), nursing staff (11), Pharmacy technical staff (10) and laboratory technicians (4). Some nurses were recruited in the paediatrics doctors' meeting, as they are family nurse prescribers and some nurses were recruited in the children's ward.

A total of 41 healthcare professionals were recruited for the post-intervention survey namely: Nine medical doctors, 14 nursing staff, 12 Pharmacy technicians and six laboratory technicians.

Demographic and clinical characteristics		Overall, N= 75	Pre-intervention N= 34	During intervention N= 41	P-value
Gender N (%)	Males	40(53.33)	18(52.94)	22(53.66)	0.951
	Females	35(46.67)	16(47.06)	19(46.34)	
Professional Background N (%)	Medical Doctor	18 (38.66)	9(26.47)	9(21.95)	<0.001
	Nurse	22 (24.00)	11(32.35)	11(24.83)	
	Pharmacy Professional staff	26 (34.67)	10(11.76)	16(29.27)	
	Laboratory professional staff	9(12.00)	4(11.76)	5(23.20)	
Highest Education level N (%)	Diploma	30(40.00)	11(32.35)	19(46.34)	0.207
	Bachelor's Degree	23(30.67)	11(32.35)	12(29.27)	
	Post Graduate Diploma	19(25.33)	12(35.29)	7(17.07)	
	BSC Honours Degree	1(1.33)	0(0.00)	1(2.44)	
	Master's Degree	2(1.33)	0(0.00)	2(4.88)	

Table 4.7: Demographic characteristics of the participants in the study

4.3.2 Knowledge, attitude and practice of health care professionals from various professional backgrounds in the pre-intervention phase

A statistically significant difference was observed in the knowledge of healthcare professionals from various professional backgrounds in both the Likert scale and multiple-choice assessments (Table 4.9). For the assessment by Likert scale, a statistically significant difference was observed between Pharmacy technicians/pharmacists and laboratory technologists ($p=0.034$) and between nurses and laboratory technologist ($p=0.029$). In the assessment using multiple-choice questions, a statistically significant difference was observed between medical doctors and pharmacists ($p=0.004$) and between nurses and laboratory technologist ($p=0.041$).

Characteristic		Medical doctors	Pharmacists/ Pharmacy Technicians	Nurses	Laboratory Technologist	P-Value
Knowledge, Mean (SD)	Likert Scale score	70.56(6.19)	67.82(6.34)	71.1(5.9)	71(1.4)	0.567
	Multiple-choice score	5.33(1.11)	4.1(1.0)	5.1(1.29)	2(2.25)	0.007
Attitude, Median (IQR)	Likert Scale score	38(36-43)	40(37-43)	41.5(37-42)	44.5(41-45)	0.3925
Practice, Mean (SD)	Likert Scale score	37(33-39)	40(38-41)	37(5.16)	36.5(35-43.5)	0.6236

Table 4.8: Knowledge, attitude and practice of health care professionals from various professional backgrounds in the pre- intervention phase

Characteristics		Medical doctors	Pharmacists/ Pharmacy Technicians	Nurses	Laboratory Technologist	P-Value
Knowledge, Mean (SD)	Likert Scale score	82.4(7.13)	75.3(7.8)	75.63(7.46)	86.6(3.13)	0.0074
	Multiple-choice score	8.4 (7.1)	5.1(2.74)	5.4(2.06)	8.4(1.34)	0.005
Attitude, Median (IQR)	Likert Scale score	44(43-45)	39(34-43)	41.5(40.5-45)	43(41-45)	0.0502
Practice, Mean (SD)	Likert Scale score	40(5.9)	47.2(7.83)	41.06(6.07)	44.8(8.67)	0.0772

4.3.3 Knowledge, attitude and practice of healthcare professionals during the pre-intervention and post-intervention phases of the study

The healthcare professionals Likert scale results between the pre-intervention and during the intervention did not indicate any significant statistical difference in the knowledge on antibiotics use and resistance (Table 4.10). An improvement concerning percentages was observed in most of the 17 questions that were included in the questionnaire to assess the healthcare professional's knowledge. Only one question had a 100%

correct response in the study, and it was observed during the intervention, the question was “Humans can be resistant to antibiotics” (Table 4.10).

Healthcare professional's knowledge on antibiotics use (Likert scale)	Pre-intervention	During intervention	P-Value
Question			
1. Different antibiotics are needed to cure various diseases, correct response n (%)	27(79)	36(88)	0.158
2. Antibiotics are effective against bacteria, correct response n (%)	32(94)	40(98)	0.934
3. Antibiotics are effective against viruses, correct response n (%)	27(79)	32(78)	0.531
4. Antibiotics will speed up the recovery of colds and cough, correct response n (%)	23(67)	27(78)	0.355
5. Antibiotics should be used to acute diarrhoea, correct response n (%)	15(44)	26(63)	0.532
6. Antibiotics shortens the duration of acute diarrhoea, correct response n (%)	14(41)	25(61)	0.324
7. If you get side effects during a course of antibiotics treatment you should stop taking them as soon as possible, correct response n (%)	16(47)	31(76)	0.222
8. If you get skin reaction when using antibiotics, you should not use the same antibiotic again, correct response n (%)	16(47)	19(46)	0.551
9. Is amoxicillin sensitive to E.coli bacteria? Correct response n (%)	13(38)	18(44)	0.427
10. Is gentamycin indicated for chronic diarrhoea, correct response n (%)?	16(47)	28(68)	0.041
11. Is Metronidazole the best drug for acute diarrhoea? Correct response n (%)	20(59)	28(68)	0.223
12. Ceftriaxone is the golden treatment for treating bacterial pneumonia, correct response n (%)	18(53)	24(59)	0.138
13. Antibiotics can cause imbalance in the body's own bacterial flora, correct response n (%)	28(82)	38(93)	0.102
14. The unnecessary use of antibiotics can increase the resistance of bacteria to them, correct response n (%)	32(94)	38(93)	0.390

15. Resistance of antibiotics is a global challenge, correct response n (%)	31(44)	37(90)	0.417
16. Using antibiotics amongst animals can reduce the effect of antibiotics amongst humans, correct response n (%)	15(44)	30(73)	0.307
17. Humans can be resistant to antibiotics, correct response n (%)	30(88)	41(100)	0.100

Table 4.10: Healthcare professional's knowledge as assessed by Likert scale during the pre- and the post-intervention phases of the study

Ten multiple-choice questions were assessed on knowledge on all the healthcare professionals in the pre-intervention and during the intervention (Table 4.11). Out of the 10 questions, three questions indicated a significance statistical difference, namely:

“A 6-year-old child has a fever of 38 °C, purulent rhinitis and angina for two days. At inspection, the throat is reddish. Which treatment do you recommend”? (**P<0.001**)

“During your ward round, you see two patients with severe renal failure. Patient A is a 4-year-old suffering from serious cellulitis at the leg, she is treated with clindamycin. Patient B is five years old with a juvenile diabetes which is empirically treated for septicaemia with ceftriaxone. Dosage reduction is needed for”? (**P=0.003**).

“Methicillin resistant - Staphylococcus aureus is susceptible to”? (**P=0.004**), (Table 4.11).

Healthcare professional's knowledge on antibiotics use (Multiple-choice)	Pre-intervention	During intervention	P-value
Question			
1. A 4-year-old girl has diarrhoea for 4 days (3 stools/day). She has no fever at examination nor during the last few days. Which treatment do you propose? Correct response n (%)	30(88)	38(93)	0.510
2. A 6-year-old child has a fever of 38 °C, purulent rhinitis and angina for two days. At inspection, the throat is reddish. Which treatment do you recommend? Correct response n (%)	3(9)	20(49)	0.00
3. During your ward round, you see two patients with severe renal failure. Patient A is a 4-year-old suffering from serious cellulitis at the leg, she is treated with clindamycin. Patient B is five years old with a juvenile diabetes which is empirically treated for septicaemia with Ceftriaxone. Dosage reduction is needed for? Correct response n (%)	4(12)	17(41)	0.003
4. Which one of the following antibiotics is safe in neonates? Correct response n (%)	26(76)	32(78)	0.871
5. Which one of the following antibiotics has the best activity against anaerobes? Correct response n (%)	28(82)	30(73)	0.344
6. Methicillin-resistant - Staphylococcus aureus is susceptible to: Correct response n (%)	7(21)	23(56)	0.004
7. Which one of the following antibiotics most effectively crosses the blood-brain barrier? Correct response n (%)	18(53)	25(61)	0.926
8. Aminoglycosides such as gentamicin are active if they are administered as follows: Correct response n (%)	21(62)	31(76)	0.135
9. At RFM Hospital, what is according to your information the estimated resistance rate of Salmonella Typhi to Cotrimoxazole (Bactrim)? Correct response n (%)	8(24)	18(44)	0.193
10. At RFM Hospital, what is according to your information the estimated resistance rate of Klebsiella to Ceftriaxone? Correct response n (%)	8(24)	22(54)	0.122

Table 4.11: Healthcare professional's knowledge as assessed by multiple-choice questions during the pre-intervention and the post-intervention phases of the study

Nine questions were directed to assess the healthcare professional's attitude on antibiotics. Even though an improvement was observed in all the questions during the intervention, there was no statistical significance difference observed between the two phases of the study, (Table 4.12). There were also eleven questions that assessed the healthcare professionals' practices and a statistical significance difference ($P= 0.004$) was observed in one question.

Healthcare professionals' attitude on antibiotics use	Pre-intervention	During intervention	P-value
Question			
1. There is abuse on antibiotics at present, correct response n (%)	30(88)	38(93)	0.378
2. Antibiotics resistance became a challenge in ESwatini, correct response n (%)	28(82)	38(93)	0.017
3. Abuse of antibiotics became the main cause leading to bacterial resistance, correct response n (%)	31(91)	37(90)	0.256
4. Antibiotics resistance affects the livelihood of the community, correct response n (%)	29(85)	38(93)	0.375
5. It is necessary to get more education about antibiotics, correct response n (%)	33(97)	41(100)	0.015
6. There is a need to establish course on 'rational use of antibiotics' at university level, correct response n (%)	32(94)	39(95)	0.569
7. It is necessary to conduct evidence base research on antibiotics use, correct response n (%)	33(97)	40(98)	0.159
8. It is necessary to formulate an antimicrobial stewardship committee in the hospital, correct response n (%)	31(91)	37(90)	0.218
9. It is necessary to have continuous profession education about antibiotics, correct response n (%)	32(94)	41(100)	0.917
Healthcare professionals' practice towards antibiotics use			
10. Doctors prescribe antibiotics when having fever (>38.5°C), correct response n (%)	3(9)	21(51)	0.004
11. Doctors prescribe antibiotics for coughing, correct response n (%)	6(18)	20(49)	0.138
12. Doctors often tell patients/caregivers on how antibiotics works, correct response n (%)	10(29)	22(54)	0.954
13. Pharmacists often tell patients how antibiotics should be used, correct response n (%)	20(59)	25(61)	0.478
14. Pharmacists often ensure the right dose of antibiotic is provided to the patient, correct response n (%)	23(68)	29(71)	0.463
15. Pharmacists often give patient education on antibiotics, correct response n (%)	10(29)	18(44)	0.804
16. Doctors often prescribe antibiotics because the patient expect it, correct response n (%)	15(44)	24(59)	0.753
17. Doctors often consider carefully whether antibiotics are needed or not, correct response n (%)	16(47)	23(56)	0.050
18. Pharmacists trust doctors' decision when she or he prescribe antibiotics, correct response n (%)	14(41)	16(39)	0.302
19. Doctors trust pharmacists that they will dispense and advise patients on using antibiotics, correct response n (%)	25(74)	26(63)	0.993
20. Doctors' advice that antibiotics can be used when cough last up to two weeks or more, correct response n (%)	9(26)	20(49)	0.344
21. Patients can be provided antibiotics when they ask them, correct response n (%)	28(82)	33(80)	0.598

Table 4.12: Healthcare professional's attitude and practice during the pre- and the post-intervention phase measured using the Likert Scale

CHAPTER 5: DISCUSSION

5.1 Antibiotic stewardship programme

5.1.1 Demographic and clinical characteristics of the patients

In this study, diarrhoea was observed most frequently in children between the ages of 6-11 months, with the median age of 10 months and an interquartile range of 5-15 months as indicated in Table 4.1. This result is consistent with other studies in finding that diarrhoea prevalence is higher in younger children (Hung, 2006; Olorunfoba *et al.*, 2014; Kabayiza, 2014) and that the prevalence is highest for children 6-11 months of age, remaining at a high-level amongst one-year old children and decreasing in the third and fourth years of life (Brhanu *et al.*, 2017). In contrary to the current study findings, Thiam *et al.*, 2017, reported the highest prevalence of diarrhoea in children between the ages of 24-59 months.

In the current study there were more males (52.13%) hospitalised than females (47.87%). This finding is consistent with the previous research by Matsebula-Myeni (2014) in the same institution. In several other studies more boys were diagnosed with AGE than girls (Muhsen *et al.*, 2017, Staat *et al.*, 1991; Siziya, Muula & Rudatsikira, 2013). In a study by Banerjee (2004) more girls than boys were diagnosed with AGE.

The establishment of an ASP is inadequate to curb the emerging antibiotics resistance but putting prepared interventions in-line with the current practices/challenges for that particular setting and then measurement of the effectiveness of the ASP is critical.

5.1.1.1 Targeted antibiotic consumption (overall use and restricted antibiotics)

The expected reduction of the antibiotic consumption during the intervention phase was not achieved. This can be attributed to the fact that during the pre-intervention phase, Ceftriaxone was commonly used, and it was the only antibiotic prescribed per patient during the course of the therapy. Overusing Ceftriaxone at RFM Hospital especially in children was discussed in several DTC meetings (January, March and June) (RFM, 2015). During DTC meetings, prescribers defended their choice of antibiotic since Ceftriaxone covers both gram-

positive and gram-negative bacteria, so for them that was crucial as the child might present with an infection which was missed by the prescriber and the factor that it is provided twice daily (DTC, 2015).

The prescribers also mentioned that the administration of Ceftriaxone is easy and convenient for the nurses and they are confident that when prescribed, administration in admitted patients is definite, compared to cefazolin which should be provided eight-hourly. The prescribers' preferred choice of antibiotic is contrary to the current STG of the Kingdom of ESwatini (MOH, 2012), as Ceftriaxone is not recommended as first-line antibiotic for the most frequently observed comorbidities in patients in this particular study. The prescribers' preferences are, however, in agreement with the results of study by Friedman (2013) in which it was established that a prescribing pattern is influenced by several factors, one of which is the ease and practicality of administration of a treatment. Friedman's (2013) findings are consistent with those of Medved (2013) who identified the medication factors, environmental factors and patient factors, predicting the occurrence of medication administration time errors by registered nurses in an acute care setting in Canada. The results of his study indicated that time criticality was one of the independent predictors of medication administration delivery time errors in the research setting (Medved, 2016).

In the current study, a significant decrease in the consumption of antibiotics was expected because the prescribers were availed of the antibiotic prescribing guidelines, stipulating clear criteria on when to use an antibiotic. No significant decrease in the total number of antibiotics prescribed was observed. This finding is contrary to various studies, indicating a decrease in antibiotic use after implementing ASP programmes (Cairns *et al.*, 2013; Mercer *et al.*, 1999; Bassetti *et al.*, 2000; Berlid *et al.*, 2001; Ansari *et al.*, 2003; Siddiqui *et al.*, 2007; Cheng *et al.*, 2009; Teo *et al.*, 2012; Michaels *et al.*, 2012; Hagert *et al.*, 2012; Storey *et al.*, 2012; Vettese *et al.*, 2013 and Principi *et al.*, 2016). A change towards a reduced use of Ceftriaxone was observed; it was restricted in AGE during the intervention phase and there was a shift towards the overuse of gentamycin and Metronidazole in the intervention phase.

When implementing the ASP during the intervention phase, patients received a combination of at least two antibiotics per admission, which were mainly a combination of Metronidazole and Gentamycin. These two antibiotics were not restricted for AGE in the intervention phase of the study and prescribers were not limited to them concerning prescribing. Although the prescribing guideline facilitated during the intervention phase, explained that antibiotics were not recommended for acute diarrhoea but only in persistent and chronic

diarrhoea, or when accompanied by sepsis (RFM, 2016), doctors prescribed antibiotics for all patients eligible for hospitalisation. The research established that prescribers relied on the laboratory investigation to determine if antibiotics can be excluded from the treatment and all were patients put on antibiotics awaiting laboratory bacterial culture investigations. Despite the growing evidence that most bacterial AGE infections are EPEC and using antibiotics is not recommended, as in most cases, EPEC-induced diarrhoea is self-limiting and can be effectively treated with ORT (Ochoa, 2011; Pawlowski, Warren & Guerrant(2011). Ochoa *et al.* (2011) report that EPEC may rarely produce persistent infections, which may require antibiotics.

A statistically significant reduction ($P < 0.001$) was observed in using restricted antibiotics. Using Ceftriaxone decreased during the intervention phase, as it was a restricted antibiotic, which required approval from the pharmacist after the prescriber had completed the restricted antibiotic form. The significant decrease in using Ceftriaxone suggests that restricting some antibiotics could be an effective intervention in preventing abuse of some antibiotics. This result also suggests that the abuse of Ceftriaxone was since there was no proper managing antibiotics and that close monitoring of antibiotics use can limit inappropriate use of antibiotics. Restricted antibiotics were identified as a crucial strategy for effective ASPs in other studies (Rahal *et al.*, 1998; Paterson, 2006; Busing, 2011; Carling, 2012).

In the current study, there were only six patients for whom antibiotics were not prescribed on admission, but these were later recommended by the ward doctor who based his recommendation on the persistence of the diarrhoea, which continued despite the rehydration conducted and using medication like the zinc tablets and other supplements. All six patients to whom antibiotics were not prescribed were admitted by the same doctor. During the steering committee meetings that were held every Thursday, the prescriber who did not prescribe the antibiotics on admission, criticised the stewardship team on adding antibiotics to the patient's therapy. Most of the prescribers indicated that in their opinion it was crucial to treat the patients with antibiotics, but they were not specific on which antibiotic should be used.

The high percentage of antibiotic use was not influenced by implementing the ASP, attributable to the prescribing doctors' reluctance to not use antibiotics in the children admitted with AGE. They did, however, stop antibiotics in response to antibiotic stewardship recommendations and this resulted in a decrease in DOS intravenous therapy. The researcher had expected implementing the ASP to bring about a decrease in the total number of antibiotics prescribed to patients (whether restricted or not), in keeping with the

literature, but it failed to change the prescribing habits of the prescribing doctors. It is possible that the unavailability of an infectious disease (ID) physician and a microbiologist in the team contributed to this pattern. The researcher supports the notion that an effective ASP requires a multidisciplinary team including an ID physician, a microbiologist and a clinical pharmacist with infectious diseases training. Putting together such a multidisciplinary team is not always feasible in low-income countries like ESwatini. There were measures that were successful, however, as discussed below.

5.1.1.2 Days of therapy and duration of hospitalisation

A statistically significant decrease in the duration of hospitalisation was observed during the intervention phase compared to the pre-intervention phase. There are several factors that could have contributed to the decreased DOT and duration of hospitalisation. It was provided by instances where conversion from intravenous to oral therapy was introduced during the intervention phase, proper hydration of dehydrated patients and appropriate managing SAM. Elliot (2010), indicated that increased rates of admission of children with gastroenteritis is exacerbated by malnutrition as a comorbidity and electrolytes disturbances. The results and the outcomes of implementing the SAM guidelines will be discussed later in this chapter. Bruzzese, Giannattasio & Guarino (2018), also indicate that hospitalisation was associated with antibiotics prescriptions.

The shortened DOS IV therapy in the intervention phase enabled ward doctors to discharge patients after the two to three days and ward doctors had an option to discharge patients with an oral therapy. The researcher observed that the doctors did not see a need of continuing the patients with oral therapy for over three days in several cases, as the patients responded well to the therapy and there were no signs of infections.

These results are consistent with other studies that indicated a decrease in days of hospitalisation and DOT in cases where conversion from IV to PO therapy was facilitated and when adherence to treatment guidelines were demonstrated (Cyriac & James (2014); Akpan *et al.*, 2015; Tejaswin *et al.*, 2018; Ng *et al.*, 2008). The conclusion that can be drawn from this, suggests that days of hospitalisation are influenced by the DOT, in turn influenced by the drugs formulation received by the patients. Patients who are on oral therapy have a possibility of an early discharge compared to patients on IV therapy, because oral therapy can be provided

at home. In the past there has also been the conventional way of prescribing antibiotics for a specific number of days, for example for 5 days or 7 days, explaining why several patient admissions lasted for five or seven days. Eliminating antibiotics therapy, as suggested in the AGE guidelines, can decrease the days of hospitalisation. The socio-economic factors associated with AGE and SAM was studied in LMICs (Hamer *et al.*, 1998; Hugh, 2006; UNICEF, 2007).

5.1.1.3 Cost of antibiotic therapy

Although a statistically significant difference was not observed between the two phases of the study, a cost decrease was observed. The researcher measured the cost of the antibiotic provided, but other costs such as the cost of medical supplies and professional costs were not measured. In the pre-intervention phase, most patients received intravenous therapy throughout the period of hospitalisation which had a minimum of 5 days. They received Ceftriaxone injections which come in a powder form and require sterile water for reconstitution, intravenous administration sets, syringes, needles and a compactible intravenous fluid. If the cost of these supplies had been taken into consideration when calculating the cost of antibiotic therapy, the difference in cost would have been even higher.

The ethical aspect of considering cost versus the best interest of the patient when rendering decisions about treatment was argued informally in the hospital DTC meeting (RFM, 2016). Early switch of the patients from IV therapy to PO therapy, contributed to the considerable decrease in the cost of the antibiotics therapy. Besides lower drug cost, costs of medical supplies and staff support are higher for IV than oral therapy, although these have not been assessed in the present study.

Although cost saving was not initially the main aim of the antibiotic stewardship programme, high cost savings related to antimicrobial use are often used to justify ASPs (Dodds Ashley *et al.*, 2014). The budget of pharmaceuticals and medical supplies in ESwatini was decreasing after several years. The ESwatini MOH and politicians are considering measures that can be put in-place to decrease the budget of medicine without compromising patients' clinical outcomes. In view of the results and the literature on the benefits of switching from IV therapy in ASP (Fischer *et al.*, 2003; McLaughlin *et al.*, 2005; Lee & Lindstrom 2007 and Tejaswini *et al.*, 2018), the RFM Hospital administrator and Senior Medical Officer is advised to support establishing ASP in the hospital and expand the programme to the entire hospital and to the 20 associated community clinics.

Since antibiotic stewardship needs a lot of funding (mainly for laboratory tests and trained personnel) proving that they can save costs might render hospital managers support that establishment and implementing ASPs. Other studies reported significant cost savings brought about by ASPs demonstrating the importance of ASPs in LMICs (Mercer *et al.*, 1999; Bassetti *et al.*, 2000; Berlid *et al.*, 2001; Ansari *et al.*, 2003; Siddiqui *et al.*, 2007; Cheng *et al.*, 2009; Teo *et al.*, 2012; Michaels *et al.*, 2012; Hagert *et al.*, 2012; Vettese *et al.*, 2013 and Principi *et al.*, 2016).

5.1.1.4 Proportion of inappropriate antibiotic courses

The patients that were eligible for the ASP enrolment, had one of the following variables.

- **Inappropriate indication**

The appropriateness of the indication of the antibiotics was measured using the four variables, fever; leucocytosis with neutrophilia and left shift, toxic granulation; raised inflammatory markers and specific organ dysfunction. More than half of the patients in the pre-intervention phase were inappropriately provided an antibiotic on admission. An improvement in the appropriateness courses of antibiotics during the intervention phase was observed, which was a statistically significant. More than half of the patients in the intervention were eligible to be provided an antibiotic compared to only 35% in the pre-intervention who had been were eligible to be provided an antibiotic. The improvement in the intervention phase could be attributable to the quality of the patient history available during the intervention phase compared to the pre-intervention phase. For example, the prescribers in the intervention phase, diagnosed more comorbidities in the pre-intervention phase. The variable that could have misled the prescribers in prescribing antibiotics in the intervention phase is the presence of fever.

In the DTC's meeting at RFM Hospital (RFM, 2014), a paediatrician mentioned that children who come in with temperatures above 38 °C needs antibiotics as part of their treatment as fever can indicate a bacterial infection. This statement might have caused the inappropriate decision to prescribe antibiotics in the study, because most patients had fever. Fleisher & Matson (2017), indicated that bacterial infection is sometimes hard to distinguish from viral infection. Bruzzese, Giannattasio & Guarino (2018), alluded that fever is not necessarily a strong indication for bacteria, but more clinical evaluation needs to be conducted. In diarrhoea,

bacterial infections are more common in locations where there is unsafe drinking water and deficient handling of sewage (Fleisher & Matson 2017). This might be true in the region where the study was conducted, as the hospital is situated in a highly populated area, which is close to the Matsapha Industrial site (Swaziland Population, 2018; UN, 2017).

The 2nd variable used to determine appropriateness of antibiotic indication was increased white blood cells. This variable was measured in all patients who were diagnosed and hospitalised for AGE. Although the increased number of white blood cell did not confirm whether the infection was bacterial or viral, it at least provided the research the idea of a presence of infection. This variable also tends to mislead prescribers in shifting their minds towards bacterial infections.

The 3rd variable considered in establishing the rationale of initiating empirical antibiotic therapy was measuring raised inflammatory markers C - reactive protein (CRP). Although, Adelstein and Baker (2014) and Bruzzese, Giannattasio and Guarino (2018) consider measuring CRP as the most practical way to detect and monitor the presence and progress of a systemic inflammatory response, in our current study, our laboratory could not measure CRP, attributable to a lack of modern equipment that can measure the CRP. The researcher considered to measure this variable in the intervention phase, as she was misled by the laboratory technologist that there is a laboratory machine that could measure CRP. The researcher believes that if CRP measurements were conducted in the hospital, it could have assisted the ASP in better recommendations of modification of therapy. Considering the importance of the CRP measurement, the research has motivated the need for measuring CRP with the laboratory and the management motivated in the MOH and currently, even though it was after the study, the hospital have a new machine that can measure the CRP.

The 4th variable considered, was organ dysfunction. The main organ taken into consideration in the context of the thesis was the kidney. The kidney function tests were performed in every patient diagnosed with AGE on admission. This test and a liver function test were mandatory if the patient had SAM as a comorbidity.

- **Inappropriate dosage**

The correct dose was appropriately conducted in both phases of the study. In the study only 16.43% cases had an inappropriate dose prescribed. There were no significant differences observed in the two phases of

the study. The importance of prescribing the correct dose was discussed by several authors (Rello, 2007; Dryden *et al.*, 2011; Ghosh *et al.*, 2014 and Bielicki *et al.*, 2015). A challenge experienced during the intervention phase was the administration of the antibiotics at the correct dosing interval. Although there was an improvement and a statistically significant difference observed during the intervention phase, the number of cases (42/125, 33.60%) in whom the correct dosing interval was not adhered to is still considered too high. An intervention is needed to improve adherence to the appropriate dosing interval. The antibiotics that were not administered at the correct dosing interval were mainly those that were prescribed three times daily. During the intervention phase, when nurses were asked and advised about the dosing interval, most of them had no idea of their wrong doing. They thought three times a day mean morning, afternoon and night versus eight-hourly dosing.

Another dosing interval challenge was managing the first dose time provided at the point of admission (Outpatient department or emergency room). The nurses at the wards did not consider the time of the first antibiotic dose, for example, a patient admitted at 16:00hrs would also get another dose at 20:00hrs as a standard time for administration of medicines in the wards.

Non-adherence to the dosing intervals of antibiotics prescribed three times daily could also be attributed to the nurses' standard shifts in the hospital. The four standard shifts have an hour of reporting exercise and then administration of medicines. Two from the four shifts start at 07:00hrs which renders and the standard first dose is at 08:00hrs after the reporting section. The staff will be more during the day and at second dosing is 14:00hrs, the third dose is at 20:00hrs after the evening shift report.

The researcher reported the challenge regarding adherence to the correct dosing intervals and made a formal request from the Chief Nursing Matron to change the nurse's shift to correctly dose the patients, but during the study period, the nurses' day and night shifts could not be changed. The medication errors arising from nursing care was appraised by Smeulers *et al.* (2015), where he mentioned that one-third of all medication errors causing harm to hospitalised patients occur in the medication preparation and administration phase, which is predominantly a nursing activity.

- **Antibiotic-bacteria mismatching (bacteria/drug mismatching)**

In the current study, there were less cases where their antibiotic-bacteria mismatching was observed. The researcher established it challenging to ensure that the bacteria/drug mismatching was appropriately evaluated in this study, because there was a limitation of blood culture from the laboratory department. With the data and the analysis done, the research could not determine the inappropriateness of the antibiotic/documentated infection.

- **Inappropriate antibiotic selection for documented infection**

The researcher could not measure the appropriateness of antibiotics for documented infection as it lacks an institutional antibiogram. An antibiotic recommended primarily (acute gastroenteritis guideline) for treatment of bacterial diarrhoea is cotrimoxazole. The researcher did not expect the prescribers to prescribe cotrimoxazole, as sensitivity studies in this hospital have indicated 100% resistance in *E.coli* cultured from the stools of hospitalised patients that were treated with AGE in this hospital, in a quality improvement study. Although cotrimoxazole is a safe drug to use in paediatrics and covers a lot of bacteria and may treat several conditions, its value in treating other conditions, except as prophylaxis for HIV/AIDS, has declined. Overusing cotrimoxazole in the hospital could have caused the high resistance observed.

In the current study, appropriateness concerning antibiotic treatment in managing SAM was observed. The clinical guidelines stipulate empirical treatment with Ceftriaxone for cases of AGE with SAM as comorbidity. In AGE cases with SAM as a comorbidity, Ceftriaxone was not considered as a restricted antibiotic. All patients that were diagnosed with SAM were provided Ceftriaxone therapy at the maximum dose.

The researcher was challenged with using Ceftriaxone in pneumonia during the intervention phase. The prescribers filled the restricted antibiotic prescribing forms in cases of Ceftriaxone prescription for pneumonia, but the reason they offered was the unavailability of blood culture to determine the bacteria that caused the pneumonia. The hospital also lacks an antibiogram that can inform the common bacteria established in pneumonia. An unresolved argument in the hospital and amongst members of the ASP committee was using amoxicillin and amoxicillin-clavulanic acid in treatment of pneumonia in children that had AGE as a primary diagnosis. Because of the side-effect of penicillin to cause diarrhoea prescribers had

reservations regarding using the amoxicillin and amoxicillin- clavulanic acid for these cases. Another reason offered by prescribers was the fact that amoxicillin is extensively used for URTIs and its overuse is thought to be linked to resistance that was indicated in a quality improvement study by the DTC.

- **Prolonged duration of therapy**

During the intervention, prescribers adhered to the prescribing a 3-day course of antibiotics and prescribed them for longer periods in cases where there was a comorbidity, i.e. SAM or pneumonia. The researcher together with the ward doctor made recommendations when the antibiotics therapy was prolonged unnecessarily.

5.1.1.5 Antibiotics stewardship recommendations

During the intervention phase, recommendations aimed at ensuring the appropriate use of antibiotics during accompanied ward rounds (section 3.3.6.3). There were 150 recommendations made for 94 of the 126 patients who were included in the intervention phase. In some cases, more than one recommendation was made in a patient. The higher percentage of recommendations made during ward rounds suggests an intensive commitment of the healthcare professionals during the ward rounds and it may also reflect that the admitting doctors did not do due diligence in appropriately prescribing and assessing the antibiotic therapy. The researcher introduced and measured interventions that were realistic and easier to transmit and easier for physicians to adopt, as previously facilitated by Pasquau *et al.* (2015).

The percentage (74.6%) of antibiotic stewardship recommendations made in this study was higher than the 45% recommendations made, reported by Metjian *et al.* (2008), who performed a prospective observational study to describe the use and impact of a paediatric ASP. They assessed the outcomes and compliance on empiric antimicrobial therapy decisions and recommendations to discontinue antimicrobial therapy and it was also higher than the percentage observed by Cairns *et al.* (2013) (35%), who introduced ASP in inpatients hospitalised in three metropolitan hospitals in Melbourne. The documentation of recommendations in the intervention phase allowed the ASP core team (ward doctor, pharmacists and laboratory technologist) to analyse the divergences on the managements of conditions requiring antibiotics in their therapy.

Decisions about altering antibiotic therapy were informed by microbiology results and other clinical findings. The ward doctor, pharmacist and laboratory technologist made these decisions together. There were instances where one antibiotic was changed to another depending on the drug sensitivity and other instances where the antibiotics were stopped because there was no bacterial growth. When the results were available, it was easier for doctors to accept the alteration of the therapy than when the decision had to be taken solely based on the patient's clinical status. There were cases where the patients stayed in hospital longer because there were no laboratory results obtained from the laboratory departments, so patients had to continue treatment.

5.1.1.6 *Stopping antibiotics*

During the intervention, 14% of the recommendations made in the ASP were to stop antibiotic courses and the ward doctor approved 85.71% of these recommendations. The researcher recommended that the antibiotics should be stopped because there was no indication for the antibiotics. The prescribers were reluctant to stop antibiotics in cases where the patients were still having loose stools. Other cases that made the recommendation to stop antibiotic therapy a challenge were cases where there were comorbidities. The ward doctor argued that it would be too risky to stop antibiotics when there were no negative blood cultures available to confirm the absence of the bacterial infection.

5.1.1.7 *Modifying therapy*

- **Changing dosing interval**

The most frequently made recommendation was "Change dosing interval" (28%), which is consistent with the results of a study by Principi *et al.* (2016), who also established the most frequent recommendation was related to changing of dosing interval. This recommendation was not adopted at all, as the hospital stipulated times for administration of injectable doses. The nursing department provided the nurses a schedule of three times daily which is 08:00, 14:00 and 20:00. As can be seen, the time between the first two scheduled times is 6 hours and 12 hours between 20:00 and 08:00. This was discussed earlier in the discussion.

- **Conversion from IV therapy to Oral therapy**

During the intervention phase, 26% of recommendations were related to the conversion from IV therapy to oral therapy. This recommendation was usually made between 'Day 2' and 'Day 3' of admission and it was made for patients who were supposed to continue with antibiotics therapy. The ward doctors adopted this recommendation in 71.79% of all cases. The most common reason for not adopting the recommendation was that the doctors were not sure that the patients would not vomit again.

In some instances, the recommendation to convert from IV-to-oral therapy in patients who were due for discharge was not made, an explanation provided by the ward doctor using an oral therapy for a period as short as one-day would be a waste of the drug and lead to an unnecessary increase in the cost of antibiotics. Most of the oral suspensions are 100 ml and a separate bottle is assigned for each patient. The 100 ml is usually for a treatment period of seven days and using the 100 ml bottle for a day and discard the bottle was not considered cost-effective. Whether implementing ASP interventions should increase using oral antibiotics as a strategy to improve outcomes and decrease costs, were deliberated in studies (Cyriac & James, 2014; Pasquau *et al.*, 2015 and Barlam *et al.*, 2015).

During the intervention phase of the study, the convenience of the conversion from IV-to-oral therapy was observed as the nurses prefer oral therapy compared to IV therapy which needed cannula insertion techniques. Even though, prescribers preferred IV therapy (measured because all inpatients were prescribed IV antibiotics therapy), the safety of conversion from IV-to-oral therapy was demonstrated by the reduction in re-admissions and improvement in clinical outcomes were observed. There was no therapeutic difference observed between the IV and the oral route. The ASP core team took into consideration the availability of antibiotic suspensions during the intervention period. This was important to ensure that a switch from IV-to-oral therapy was possible.

Based on the results of this research, it is recommended that ASPs should be facilitated to increase both appropriate use of oral antibiotics for initial therapy and the punctual transition of patients from IV-to-oral antibiotics. From discussions with ward doctors it was determined that they preferred prescribing antibiotics through IV because it ensures that patients receive the correct oral dose administration whereas accuracy of oral administration is dependent on individual nurses. The study indicated that conversion from IV-to-oral

therapy decreases the cost of the antibiotics and reduces the duration of hospitalisation and revealed that there was an overuse of IV antibiotics compared to oral antibiotics. Patients were seemingly receiving intravenous therapy just because they were inpatients.

According to Cyriac and James (2014), the overuse of injections, when oral formulations would be more appropriate, is one of the crucial factors for the irrational use of medicines. They also alluded to the fact that prescribers believe that chances of reinfection will be less if they give a complete IV course of antibiotics. As a result, prescribers usually tend to prefer IV medications during admission and continue them until patients are discharged. This behaviour was observed in the pre-intervention phase where no IV-to-oral therapy conversions were observed.

Recommendations for changing IV-to-oral administration were not made in cases where it was impossible to do so. These were cases where the clinical practice guidelines did not specify how the change should be made, for example, where there was a use of gentamycin. IV-to-oral conversion of the same antibiotic is less complicated than other strategies and is applicable to several healthcare settings (Barlam *et al.*, 2016). The authors specified that these programmes should be integrated into routine Pharmacy activities and ASPs should facilitate strategies to assess patients who can safely complete therapy with an oral regimen to reduce the need for IV catheters. Using IV catheters in administering IV injectables may cause bloodstream infections, so converting patients to oral therapy may also assist in controlling infection. The association of IV catheters with bloodstream infections was qualified by (Grady *et al.*, 2011; Hadaway 2012).

According to Cyriac and James (2014) the main obstacle limiting intravenous to oral conversion is the belief that oral medications do not achieve the same bioavailability as that of intravenous medications and that the same agent must be used both intravenously and orally.

- **Shorten the duration**

During the intervention, recommendations to shorten the duration of antibiotic treatment constituted 4.67% of the recommendations and these were readily accepted by ward doctors. From discussions with ward doctors during ward rounds, the research observed that they were comfortable to shorten the therapy when

there were formed stools. In cases where there was a de-escalation of antibiotics, there was no evidence of untoward effect.

Although prescribers were guided to prescribe antibiotics for three days during admission and that the ward doctor would recommend whether there was a need to continue treatment, most prescriptions were for at least five days and seven days at most. The rationale for the prescribed DOT could not be established.

The study findings are in agreement with other studies (Masterton, 2011; Camargo, 2013) that shortened antibiotic treatment of three to four days could be adequate for most bacterial infections. It is acknowledged that there are exceptions though. It was impossible to assess possible reduction in resistance, attributable to the limited duration of the intervention phase when discussing the limitations of the study. A suggestion for future studies could be to evaluate the effectiveness of the ASP over a longer period, whilst at the same time expanding it to more cover IDs.

Despite the evidence that shortened duration of antibiotics in otitis media, acute bacterial rhinosinusitis, prescribers were prescribing antibiotics for seven days at the RFM Hospital when these conditions were diagnosed as comorbidities to AGE (Matsebula-Myeni, 2014). There were no side effects observed in patients for whom the recommendation to shorten or stop antibiotic treatment was made and adopted. According to Hayashi & Paterson (2011) the extent to which knowledge of the efficacy of shortened durations of antibiotics for common infections was translated into changes in clinical practice is completely unknown. There is a need to determine the effectiveness of shortening the duration of antibiotic therapy. There is also a need of a quality standard laboratory for microbiology to assist prescribers by confirming the presence or absence of bacteria.

- **Alteration of dose**

During the intervention phase, recommendations to alter the prescribed antibiotic dose were also made. The pharmacist calculated the dose based on the weight of the child on admission. There were 14% of cases where the dose needed alteration, of those 14% cases, 8% were to increase dose and 6% were to decrease dose. The small percentage of incorrect doses on prescriptions suggest that the prescribers are vigilant on dosing children in accordance with their weight.

Incorrect doses were a challenge in children at RFM Hospital. The researcher, who is a pharmacist by profession, has encountered several outpatient prescriptions where there were wrong doses prescribed. An improvement in the doses per weight was observed, however and was confirmed by the relatively small percentage of incorrect doses observed during the intervention phase.

- **Special consults**

During the intervention phase, there were no cases that needed a special consult from the paediatrician.

- **Other recommendations**

During the intervention, the ASP core team followed the hand washing procedure stipulated by the hospital infection prevention and control department. The ward doctors washed their hands with water and soap after each ward cubicle and after each patient, they used the alcohol hand sanitiser produced in the hospital by the Pharmacy department. During the intervention, in 80% of cases, the ward doctors, documented the instruction to nurses to discontinue treatment and removal of the IV catheter, thereafter.

5.1.1.8 Patient outcomes

- **Development of subsequent infections**

No subsequently developed infections were observed during the intervention phase. The researcher took cognisance of prescribers' fears about altering antibiotics therapy from the doses and durations prescribed in the clinical practice guidelines. Developing subsequent infection was measured, especially in patients for whom there was an alteration of therapy, i.e. dosing alterations, stopping the therapy, conversion from IV-to-oral therapy and changing of antibiotics.

Although not several studies measured developing subsequent infection after altering of antibiotics therapy from the conventional therapy, some studies, articulated below, have proved that exposure-reducing strategies do not compromise patients' clinical outcomes. In a study by Metjian *et al.* (2008), only three of

the 84 (3.5%) patients for whom alternative therapy was recommended, developed an infection not covered by the ASP recommendations or the antibiotic initially requested by the clinician.

Contrary to the above findings, a study by Lee & Lindstrom (2007), where a guideline of IV-to-oral conversion was introduced, and an early discharge was performed, led to a thirty-day readmission rate of 6%. These findings suggest that there should be a close monitoring in patients where the dosages are altered. Although in the current study there was no development of subsequent infections, a study should be conducted to measure developing subsequent infections in confirmed bacterial IDs.

- **Readmission for acute gastroenteritis**

During the intervention phase the number of re-admissions for AGE decreased compared to the pre-intervention phase. A statistically significant difference was observed between the two phases of the study. This were possibly caused by the improved managing AGE provided by implementing the clinical guideline for the diagnosis, treatment and managing AGE and its comorbidities during the intervention phase. This was a positive outcome of the study as there was only one readmission during the intervention phase which suggests that there was proper managing AGE and its comorbidities. In the current study, patients that were re-admitted were those that had SAM as a comorbidity. This could be explained by Gupta (2014), as he mentions that each episode of diarrhoea deteriorates the nutritional status of the body necessary for growth and development children.

- **Mortality**

Fewer deaths (15 deaths; 11.9%) were observed during the intervention phase than during the pre-intervention phase (30 deaths; 21.6%). This is an important and significant emphasise of the study, as reducing child mortality is one of the MDGs (Siziya, Muula & Rudatsikira, 2013). The proper utilisation of ORS during the intervention phase and managing adequate hydration could possibly have contributed to the decrease in the number of deaths. Our study mortality results are comparable with results published by Thiam *et al* in 2017.

The major cause of death in the pre- intervention phase was SAM (21 deaths), followed by AGE (13 deaths). There were no good records on the hydration status of these patients. There were also nine deaths of patients who had comorbidities of sepsis, pneumonia and bronchitis and seven deaths in patients with severe dehydration. Interestingly, during the intervention phase, all the patients who passed away were those who presented with SAM and most of them were re-admissions of malnutrition cases.

Gupta (2014) indicate the link of several episodes of diarrhoea, malnutrition and mortality. The patients who passed away of SAM in the pre-intervention phase, were not assessed whether they were re-admissions or not. Two patients passed away within an hour of admission and these were excluded from the number of deaths as the patients were not included in the intervention phase of the study. The current study results are consistent with Bruzzese, Giannattasio, Guarino (2018) that indicated the association of SAM and increased mortality. The author also mentioned that patient with AGE were significantly more likely with malnutrition and the status of the malnutrition is the only independent factor associated with an infection.

The decrease in mortality observed during the intervention phase was a positive outcome of the intervention and was probably related to better managing children with AGE, an increased awareness and implementing unique treatment requirements of severely malnourished children, as Bruzzese, Giannattasio, Guarino (2018), recommended that patients with SAM should be treated differently and the antimicrobial therapy should be aggressive.

Although the intervention resulted in a decrease in the percentage of deaths, the deaths attributable to diarrhoea and malnutrition observed in the study was higher than that recommended by (Sphere project,

2003) (less than 10%). It also fell short of WHO suggestions of less than 5% (WHO, 2013). These findings suggest that SAM is the major cause of death in patients that present with AGE as a primary diagnosis. It also suggests that proper managing dehydration in AGE has positive clinical outcomes.

5.2 Conclusion: Effectiveness of the ASP

Implementing the multifaceted ASP interventions improved the diagnosis and treatment of infections during the intervention phase. The study also reduced child mortality during the intervention phase, which is one of the MDG's (Siziya, Muula & Rudatsikira, 2013). The successful implementing AS strategies had a significant impact on reducing targeted antibiotics use, improving quality of care of hospitalised patients and preventing the emergence of resistance. Not all challenges related to implementing AS programmes in paediatric settings are solved. The most important remaining challenges involves educating prescribers on the unnecessarily prescribing on the non-targeted antibiotics as decreasing the use of antibiotics was not achieved.

Prior approval of using restricted antibiotics by the pharmacists for AGE and its comorbidities, combined with the daily ward rounds that were by the ASP core team resulted in a better managing patient admitted for AGE and received antibiotics as part of their therapy. Prescribers adopted recommendations that were made by the pharmacist and the laboratory technologist during the ward round. Some resistance to change therapy was documented for younger patients. Prescribers did not change their belief that antibiotics should be prescribed to children requiring hospitalisation for acute gastroenteritis, which is not recommended in the AGE guidelines and other global guidelines on treatment of AGE presenting with or without dehydration. In spite of an ASP intervention, there was high use of antibiotics in children presenting with AGE, which is not in keeping with other studies. Our findings provide a useful baseline for ASP intervention and comparison with other future national, regional and global studies.

5.3 Recommendations: Effectiveness of the ASP

The interventions that were facilitated are labour intensive, so it is recommended that the hospital should have a full-time pharmacist to do antibiotic stewardship activities and participate in wards rounds full-time. A sustainable audit and feedback mechanism should be put in-place. There is also a need of implementing

an ASP in other hospitals in the country and intervention results should be documented, monitored and compared. Expansion of postgraduate programmes for prescribers, pharmacists/Pharmacy technicians, laboratory technologists and nurses in paediatrics IDs.

Successful antibiotics stewardship interventions need to be further identified and facilitated in hospitals. The recently finalised “National Action Plan for Combating Antibiotic-Resistant Bacteria” should encourage the formation of ASPs and strongly encourages these programmes to include paediatric patients, in the interest of decreasing the incidence of antibiotic-resistant bacteria and improving health care for children. We further recommend that hospital administrations support these programmes and agree with legislative and reimbursement initiatives for ensuring their presence.

5.4 Bacterial causes of acute gastroenteritis and antibiotic sensitivity

The current study revealed that most the patients presented with *E.coli* as the bacterial cause of AGE. It could not be established whether the other causes of AGE were viral. The reason for determining whether the major cause of AGE was bacterial, was that antibiotics were prescribed for almost all patients diagnosed with AGE with or without comorbidities. Although (Elliot, 2010) indicated that it is not necessary and practical to perform stool specimen for children presenting with acute gastroenteritis, the research required all stool specimen of children prescribed antibiotics to be tested for the presence of bacteria. The researcher wanted to use these results as a motivation to prescribers not to prescribe antibiotics in children with AGE, when the results have proved so.

Although it is known that most gastrointestinal illnesses are self-limited and managing dehydration in AGE is the golden treatment, certain risk factors such as malnutrition, immunosuppression and young age rises developing diarrhoea and can complicate managing AGE (Elliot, 2010). In the current study, Enteropathogenic *E.coli* was the most diagnosed bacterial cause of AGE in the intervention phase. Our results are consistent with Bruzzese, Giannattasio & Guarino (2018), where he established that four agents (rotavirus, Cryptosporidium, enter toxigenic *Escherichia coli* (ETEC) producing heat-stable toxin and Shigella) account for most cases of infectious diarrhoea in African and Asian children younger than five years old. There was study was running concurrent with our study and revealed that rotavirus was established in 42% of the patient presenting with AGE.

The most frequently observed clinical features were vomiting and fever in the current study. Bruzzese, Giannattasio & Guarino (2018), mentioned that bacterial infections may be associated with the presence of specific clinical features, notably fever, abdominal pain, blood in the stool and faecal leukocytes, which was not observed in the current study and most importantly in the pre-intervention phase, when patient examination was properly conducted. The presence of faecal leukocytes was not measured in the stool. None of these features are reliable to support a bacterial aetiology, although it is known that faecal leukocytes are not commonly observed in diarrhoea caused by virus and parasite Bruzzese, Giannattasio & Guarino (2018).

In the current study, the infection rate was higher amongst children of age 5-15 months and slightly higher amongst males compared to females. It is extensively documented that contact with diarrhoeal pathogens in developing countries is related to the age of the child (Fletcher, McLaws, Ellis (2013), Mekonnen, 2015 and Bruzzese, Giannattasio & Guarino, 2018). There was no association observed between age and gender of the child with the isolated enteric bacterial pathogens. The findings of the current study are consistent with the findings obtained by (Mekonnen, 2015) who established the predominant age bracket to be 6-24 months and male predominance. This was also established in a study conducted in Nepal, in which the infection rate was highest in the age group of 6-24 months and the 78.3 % of diarrhoea cases were observed in boys (Ansari *et al.*, 2012).

The European Society for Paediatrics Gastroenterology, Hepatology and Nutrition/European Society for Paediatrics IDs evidence-based guidelines for managing acute gastroenteritis in children support the use antibiotics in patients less than six months of age, although there is no good evidence (Guarino *et al.*, 2014). The guidelines stipulate that for infants under three months of age, microbiology should always be obtained, and antibiotics treatment should be considered. The guidelines recommend that if diarrhoea is severe or there are signs or clinical symptoms of general infection, or if symptoms are worsening after three or more days from their onset, antibiotic therapy should be started. Although there were few children below the age of six months in our study, the ones that were enrolled were covered with antibiotics as Dr Getahun, the paediatric specialist from our hospital once articulated that the condition of younger children can change drastically, so the cover with antibiotics is important (Mavundla *et al.*, 2015).

In the current study, most isolated bacteria were EPEC, which is consistent with other studies with also indicated that EPEC is the main cause of diarrhoea identified in developing countries (Qadri *et al.*, 2005,

Ochoa *et al.*, 2011 and Taru Singh *et al.*, 2017). In South Africa, it was indicated that 40% of infantile diarrhoea could be accredited to EPEC (Aslani, 2009).

The author agrees and can relate to the conclusion by Fletcher, McLaws & Ellis (2013) that there is a need for developing inexpensive sensitive and specific diagnostic methods to improve pathogen detection in clinical laboratories. Global support is necessary for equitable access to rotavirus vaccines in developing settings and for continued research and development of cost-effective interventions to prevent and control diarrhoeal illnesses global.

The prescribers at RFM Hospital prescribed antibiotics in acute diarrhoea even in cases where there were no comorbidities present in both phases of the study. Using fluids in managing AGE is supported by the evidence that most non-bloody diarrhoeal episodes in children under five years of age in low-income settings are self-limiting and are caused by viral pathogens (*rotavirus*, *norovirus*, *astrovirus* and *enteric adenovirus*) or pathogens for which antibiotics are likely of limited efficacy or even dangerous (e.g. *Salmonellae* and *Campylobacter*). These findings are also supported by the study performed at RFM Hospital.

5.5 Microbiology results

The most frequently isolated bacteria in this study were *E. coli*, *Klebsiella* and other gram-negative bacilli, two cultures yielded gram-positive bacilli, one of which was a CSF culture. Positive stool cultures were interpreted as being indicative of enteropathogenic organisms. Although EPEC are of public health significance, they are not routinely diagnosed as enteric pathogens in clinical laboratories (Garcia *et al.*, 2009). Their incidence in children under 2 years of age and importance in community-acquired diarrhoea is generally unknown (Garcia *et al.*, 2009). Lanata *et al.*, (2013) and Ochoa *et al.*, (2011) claim that EPEC is a substantial cause of infectious watery diarrhoea often accompanied by fever, vomiting and dehydration in children under 2 years of age. In the current study positive *E. coli* cultures were interpreted as EPEC.

The stool culture results are comparable to studies by Akingbade *et al.*, (2014) where (54%) yielded growth of *E. coli* and another study by Galadima & Kolo (2014), where *E. coli* bacteria was identified in 84 cases (47.734%). Other studies by Behiry *et al.*, (2011) and Mekonnen (2015) *E. coli* was also the most commonly cultured organism (5.6% and 12.8%, respectively), but the percentage was lower than in the current study.

The prevalence rate of *E.coli* infection was higher than in most studies from low-to-middle-income countries: Iraq (25.9%; Alrifai *et al.*, 2009), Nepal (22.8%; Jeevan *et al.*, 2009) and Ethiopia (12.8%; Mekonnen, 2015). These findings suggest that *E.coli* is the most cultured bacteria in AGE patients. Although the presence of *E.coli* does not suggest that the bacteria is infectious and there is a need of antibiotics, but these results will assist the hospital in informing the empirical treatment of bacterial diarrhoea.

Bacterial culture and surveillance of viral infections were considered to be the most important step leading to diagnostic certainty in the RFM Hospital. Although the research perceived viral infection to be the most possible cause of AGE, most prescribers believe that bacteria were a cause of the diarrhoea, hence the prescribing of antibiotics for all AGE patients. The researcher concentrated on bacterial culture to stop using antibiotics where it was necessary. The researcher is of the opinion that if a clinician can lead the ASP core team, the greater decrease in using antibiotics could be brought about than from an intervention lead by a pharmacist as was the case in this study. More details on the perception on antibiotics use will be discussed in the later sections. Principi *et al.* (2016) emphasised that the challenge of selection of the correct antibiotic regimen for a child is related to the lack of bacterial evidence. In the current study the research's results were limited by the lack of rapid diagnostic tests and the prescriber waited for 24 hours before confirming the presence of the bacteria in the stools.

5.6 Sensitivity results

In the current study, intervention phase, *the E.coli* resistance rate to Ceftriaxone was 76.5%, cotrimoxazole (83.3%), chloramphenicol (62.5%) and amoxicillin (88.9%). Cultured *E.coli* isolates were sensitive to gentamycin (54.6%), nalidixic acid (50%) and ciprofloxacin (55.6%). These results were expected to be slight less than the observed as these drugs are not extensively used in the hospital and they are sensitive to gram-negative bacilli. These results indicate lower sensitivity to nalidixic acid than in a Nigerian study, in which 73.3% of *E. coli* cases were sensitive to nalidixic acid (Kandakai-Olukemi, 2009). The results suggest that antibiotic resistance is a challenge in the hospital and if major interventions are not put in-place, antibiotics in the hospital will be of no use and we would not have any antibiotics for severe infections and ICU cases. Bruzzese, Giannattasio & Guarino (2018), mentioned the recommendation of shortened duration of antibiotics therapy in severe cases of AG, but also indicated the emerging challenge of antibiotics resistance also observed in the current study results.

No bacterial cultures were performed during the pre-intervention phase, which made it difficult to compare the relevance of using antibiotics during the pre-intervention phase to their use during the intervention phase. The inclusion of routine stool cultures as part of the multifaceted intervention assisted prescribers and the ASP core team in appropriate diagnosis and treatment of the AGE and its comorbidities.

The Infectious Disease Society of America (IDSA) suggests rapid infection diagnostic testing to conventional culture and routine reporting in infectious diseases (IDSA, 2006). Although this might be possible in developed countries, the limited resources in developing countries renders it difficult to have rapid infection diagnostic tools. The RFM Hospital has inconsistent availability of laboratory diagnostics and in ESwatini out of stock of laboratory diagnostic devices are considered to be less important than out of stock of medicines and medical supplies. This was confirmed by a task team appointed by the Prime Minister to look into the issues of medicines out of stock, during the same period that the country was not performing CD4 counts in patients diagnosed with HIV.

Our study results are also consistent with Theren (1988), that most gram-negative bacteria, including EPEC are sensitive to gentamycin and nalidixic acid and for that reason it may be a better choice than Ceftriaxone, as Ugwu *et al.* (2017) observed a low susceptibility of diarrhoeal organisms with third-generation cephalosporin (Cefuroxime and Ceftriaxone). The same result was indicated by Kibret *et al.* (2011) who concluded that nitrofurantoin, gentamicin and ciprofloxacin are considered appropriate for empirical treatment of *E. coli*. Regular monitoring of antibiotic susceptibility was recommended.

The sensitivity testing results obtained during the intervention phase suggest that bacterial gastroenteritis at the RFM Hospital can be treated with nitrofurantoin. Nalidixic acid had the highest level of susceptibility of all the antibiotics tested in positive *E.coli* cultures followed by nitrofurantoin, followed by ampicillin, amoxicillin, cotrimoxazole, Ceftriaxone, gentamycin and Metronidazole. Nalidixic acid and nitrofurantoin are currently not included in the ESwatini standard treatment guidelines and essential medicines list. Nitrofurantoin is a broad-spectrum bactericidal antibiotic that, through a complex mode of action which is not completely understood, affects both gram-negative and gram-positive bacteria (Munoz-Davila, 2014). In studies that were reviewed by Munoz-Davila (2014) activity against *E. coli* non-ESBL is excellent

A six-month study, in a private practice set-up, 109 children with a mean age of 2.61 years, who were admitted to the hospital with acute bacterial diarrhoea diagnosed on the basis of clinical findings and faecal leucocytes over 10/high power field, were treated with nalidixic acid, established that nalidixic acid was an effective and safe antibiotics in acute infectious diarrhoea. It cut down the days of hospitalisation and cost. It was well tolerated even in children less than 3 months (Paramesh 1990).

Diniz-Santos *et al.* (2006), share the sentiments with Paramesh (1990). He alluded that nalidixic acid is the only non-fluorinated quinolone available initially considered the best option to replace ampicillin and TMP-SMX in treating acute bacterial diarrhoea.

5.7 Conclusion: Bacterial causes of AGE and antibiotic sensitivity

The study revealed that the EPEC was the commonly isolated bacteria and the causative agent for acute bacteria gastroenteritis in children less than five years at RFM Hospital and most these were established amongst children less than 24 months of age. The study also revealed that there is an elevated antibiotics resistance to EPEC at RFM Hospital. An elevated resistance was observed in antibiotics that were commonly used in the hospital mainly amoxicillin, cotrimoxazole, Ceftriaxone, cotrimoxazole and chloramphenicol. Surprisingly, there was a resistance in nalidixic acid which was not used in the hospital and other public hospitals. Drug susceptibility testing revealed that gentamicin, nalidixic acid and ciprofloxacin were more likely to be effective against EPEC than Ceftriaxone, cotrimoxazole and amoxicillin, respectively. Metronidazole was established to be intermediate.

Nalidixic acid is available in private pharmacies but the research is not aware of the magnitude of use of the antibiotic. Childhood diarrhoea caused by enteric bacteria remains an important health concern in the study community. These findings provide useful information to the hospital laboratory in its endeavours to have an institutional antibiogram.

5.8 Recommendations; bacterial causes of AGE and antibiotic sensitivity

Gentamicin and nalidixic acid may be prescribed as effective antibiotics to treat diarrhoea. Although gentamycin therapeutic drug monitoring (TDM) is a recommendation, the RFM Hospital is not equipped to

perform TDM of aminoglycosides and therefore, this recommendation could not be facilitated, but may be considered for future studies. Care giver should be educated on the bacterial causes of diarrhoea and proper sanitation should be encouraged. Children should always be provided clean water. The hospital laboratory needs to improve its microbiology desk, as the technicians were unable to classify a significant number of the gram-positive and gram-negative bacteria. It would be helpful to recruit a microbiologist or a pathologist. EPEC should be considered the next priority for vaccine development for paediatric diarrhoeal disease, attributable to its high morbidity and mortality rates.

5.9 Compliance with clinical practice guidelines

This section discusses in depth the adherence of the clinical practice guidelines that were developed and facilitated during the intervention phase. The guidelines are as follows; antibiotic prescribing guideline, acute gastroenteritis guideline accompanied by the hydration protocol and the SAM guideline.

5.10 Antibiotic prescribing guideline

- **Appropriateness of decision to prescribe antibiotic**

The appropriateness of the antibiotic was determined by the diagnosis and the presence of any comorbidities and the suggested empirical treatment and the clinical history of the patient. The variables to determine the presence of infection was measured appropriately during the intervention compared to the pre-intervention as there were instances where relevant information was not available.

In the pre-intervention phase, 25.29% of prescriptions were deemed appropriate compared to the 54% of prescription in the intervention phase ($p < 0.001$) thus reflecting a statistically significant improvement with regard to the appropriateness of decisions to prescribe antibiotics during the intervention phase. Bruzzese, Giannattasio & Guarino (2018), established 78% cases of inappropriate antibiotics use in children with gastroenteritis, which were deviations from the WHO protocol for AGE.

The presence of comorbidities had an influence in the appropriateness of the decision to prescribe antibiotics, a good example was the presence of pneumonia, as it was difficult to determine the bacteria that

could have caused the pneumonia as there was no blood culture conducted during the intervention. The limitation of culturing blood rose from the fact that the laboratory with inconsistencies in availability of culture bottles, therefore an antibiotic sensitivity test was not performed for all cases of pneumonia. The diagnosis of pneumonia was only confirmed by X-ray.

- **Culture performed to confirm the presence of bacteria**

Although a statistically significant increase was observed in with regard to the number of stool cultures performed to confirm the presence of bacteria before prescribing an antibiotic, it was still low during the intervention phase (28%). The possible reasons for not requesting stool cultures, e.g. challenges experienced regarding the prescribers' apparent resistance to request cultures because the laboratory. In the research's observation, prescribers were not keen in requesting the stool cultures, they complained that the laboratory is unreliable and most of the time the prescribers did not trust the results from the laboratory. They also complained about the cumbersomeness of filling the microbiology stool culture forms. The other challenge experienced regarding the stool culture was the delay of nurses sending the stools to the laboratory and the laboratory technologist bring back the results of the cultured specimens.

Most of the patients in the intervention phase cultured their stool after administration of the antibiotics. Those were the patients whose stools were requested by the ward doctor. At RFM Hospital, the patients get their first dose during admission, therefore most of the time the laboratory tests will be performed in the wards. Prescribers would always blame the laboratory department of delaying results, hence admitting the patient and then request for investigation is the most comfortable route for both the prescriber and the patient.

The inadequate human resource in the laboratory was the main challenge identified as cause of the un-analysed specimens. Initially the laboratory functioned with only one laboratory technician who had the required knowledge to do bacteria cultures and sensitivity testing, but he was later joined by another laboratory technician who was passionate about microbiology. During weekends the microbiology bench was not working, and specimens taken on Fridays could therefore not be analysed in time to inform decisions about the need for antibiotic treatment.

- **Empirical antibiotic treatment**

There was a statistically significant difference ($p < 0.001$) in appropriateness of empirical treatment between the intervention phase (62.40%) and the pre-intervention phase (11.49%). Most patients were prescribed appropriate empirical treatment during the intervention phase. Patients that were considered to be provided antibiotics empirically, were severely sick patient and or with specific risk factors (i.e. immunocompromised). In the intervention phase, depending on the severity of patients, empirical treatment was started whilst awaiting the results of the microbiological investigated as indicated by (Bruzzese, Giannattasio & Guarino, 2018)

The main drug restricted because of abuse was Ceftriaxone, but it was only allowed to be prescribed as first-line treatment for patients with malnutrition. Using Ceftriaxone as an empiric treatment in the pre-intervention phase was observed, hence it was restricted in the intervention phase. Bruzzese, Giannattasio & Guarino (2018), indicated using cotrimoxazole and Metronidazole oral, but does consider using parenteral Ceftriaxone in severe cases.

The RFM Hospital does not have any local rates of resistance to various pathogens as suggested by the IDSA and SHEA (2006) that every institution should develop stratified antibiograms to assist ASPs.

Appropriate empirical treatment was observed in all patients who were diagnosed with AGE and malnutrition concurrently. The antibiotics prescribing guideline recommended using amoxicillin for pneumonia and an addition of gentamycin in children less than six months, but it was not conducted in the current study. The AGE and its comorbidities guidelines suggest that bronchitis, Laryngitis are mostly viral and there is no need for antibiotics, but in the current study, the antibiotics that were used were not the prescribed empirical treatment. In the intervention phase, there were cases of otitis media that were observed and using penicillins antibiotics as per the antibiotic prescribing guideline was not aligned to.

The researcher could not find the reason for the underutilisation of penicillin for pneumonia and otitis media, but from the quality improvement study by the DTC, the research can conclude that prescribers do not trust using penicillin for confirmed cases of pneumonia and otitis media as there was a resistance of penicillin to the cultures bacteria, although there bacteria isolated were not identifies in the quality improvement study.

According to the statistics unit, pneumonia is the second leading cause of deaths for children less 12 years at RFM Hospital (RFM, 2017), therefore prescribers tend to over prescribe antibiotics, ensuring that they do not miss an infection. Although, otitis media is not a common comorbidity but if left untreated can cause serious side effects, even in this case, prescriber tend to over prescribe antibiotics.

- **Definitive treatment after laboratory culture results**

Most prescriptions were definitive treatments in the intervention phase, namely (87.5%), whilst 12.5% of patients were provided definitive treatment in the pre-intervention phase. In the pre-intervention phase, treatment was considered definitive in cases where the comorbidities diagnosed were confirmed using diagnostic devices other than culture, for example, the presence of kidney infections was confirmed through kidney function tests which were conducted in patients which had malnutrition as a comorbidity.

The researcher concentrated mainly on stool culture results as blood culture could not be conducted in most cases as there were no blood culture bottles in the laboratory department. Murray & Masur (2012) argued that the value of blood cultures for confirming the clinical diagnosis of disseminated infection (such as meningitis, pneumonia, abdomen, urinary tract, or febrile neutropenia) from a localised focus as suboptimal. Although most untreated patients with bacterial meningitis have positive blood cultures, only 30% of patients with bacterial pneumonia and intra-abdominal infections have positive cultures. This may lead to infections not treated when definite treatment is based solely on blood culture results.

- **Evaluation of appropriateness of antibiotic treatment**

During the intervention phase, the ASP core team was mandated to evaluate the appropriateness of antibiotic treatment at 'Day 3' of the antibiotic course and the prescriber was expected to have written notes on the patient chart whether the antibiotic was still necessary, attributable to clinical diagnostics, bedside tests and laboratory tests. Using antibiotics can change, attributable to changes of the patient condition. Evaluating the patient's condition throughout hospitalisation is important especially when the patients present with multiple morbidities.

During the intervention phase, 88% of prescriptions were deemed appropriately evaluated throughout hospitalisation. Most often, the presence of persistent fever in patients influenced prescribers in favour of prescribing antibiotics as clinically, the presence of an infection raises the body temperature. This indicator is not, however, unique to bacterial infections, as body temperature can also rise in the presence of viral infections. During the ward rounds, the prescriber noted the basis of continuing the antibiotics other than the presence of one variable which cannot determine using antibiotics. Attributable to the absence of computed tomography scanning in the RFM it was impossible to diagnose whether pneumonia was bacterial or viral and the ASP core team had to rely on blood cultures which were not consistently available from the laboratory department.

- **Recommended dose prescribed**

The doctors prescribed the recommended dose in most cases. In the pre-intervention phase only 16.43 % had wrong doses prescribed. The researcher expected an improvement in the cases of correct doses but almost the same percentage on cases existed in both phases of the study. It was observed that the antibiotic doses prescribed, were either too small or too big and it could not be established how the prescribers had calculated the doses they prescribed. The doses were then adjusted during the intervention phase and the adjustments were recorded as ASP recommendations.

- **Correct dosing intervals for administration**

In the study overall, antibiotics were administered to half of the patients at the correct dosing intervals. Most of the patients (64.8%) were administered at the correct dosing interval in the intervention phase compared to the pre-intervention (39%).

- **Infection prevention and control**

Most patients that were eligible for the IV to PO switch, were converted from the IV-to-oral switch, as per the antibiotic prescribing guideline. Some patients that were eligible for the switch could not be switched because of unavailability of the oral alternative, i.e. switching from Ceftriaxone IV to Cefuroxime PO. The IDSA and SHEA (2006) strongly recommend punctual conversion from IV to PO therapy where an oral

alternative exists. The punctual conversion of the IV therapy was associated with the reduced cost of antibiotics and decreased hospitalisation days.

The conversion from IV to PO was probably the most accepted recommendation; if only the oral drugs were available and there were integrated Pharmacy activities to ensure that this recommendation is fully facilitated. The IV-to-oral switch was the accepted principle of antibiotic prescribing. The same sentiments are shared by; Storey *et al.* (2012), where he obtained a 100% implementation rate of the IV-to-oral therapy.

The prescribers self-initiated the IV-to-oral therapy without waiting for a recommendation from the research. Some patients that were not switched were those that were left with few doses before discharge, to limit the waste of the suspension. Initiating oral therapy will be the best therapy to avoid cost in eligible admission cases. The IDSA emphasised a important aspect of PO therapy being less complicated and it could be this reason that most patients eligible with being switched, were switched. The researcher fully agrees with the association. Most nurses prefer the IV route during admission in AGE because some patient especially the children turn to vomit when they have diarrhoea, so it is difficult to decide to give a second dose after vomiting especially when the vomiting did not occur immediately after provided the patient the PO dose.

- **Infection prevention and control**

The ASP intervention to control infection though removal of IV catheter right after discontinuation of IV therapy succeeded in the intervention phase compared to the pre-intervention phase. In the pre-intervention phase, no prescriber documented or provided the order to remove the IV cannulas after discontinuation of IV therapy, compared to the intervention phase where there were 80 cases prescribers documented the instruction for the removal of the IV cannulas. The researcher established cases where the IV cannulas were not removed and when the ward doctor was approached on why the IV cannulas were not removed, the ward doctor alluded to the fact that, in most cases where the cannulas were not removed was attributable to the ward doctor not feeling confident that the patients will not need the IV cannula during the admission.

Infection prevention and control is an important characteristic for combatting the inappropriate use of antibiotics and containment of antibiotic resistance. The hospital infection prevention and control unit has not made intervention in considering the removal of IV cannula as a way of preventing and controlling

hospital-acquired infections. A lot of studies have not studied the impact of early removal of IV cannulas as an integral antibiotic stewardship intervention. In our current study, even though the observations were not documented, prescribers were compiling with the hospital hand washing campaign of washing hands every after three patients, but the ward doctor had the alcohol hand rub that he used to spray every after each patient.

5.11 Guideline on the Diagnosis, treatment and managing AGE (accompanied by the hydration protocol) and its comorbidities

Diarrhoea remains the most common cause of admissions at the RFM Hospital amongst children under five. This was observed in the comparable number of admissions in the pre-intervention and during the intervention phase. This is similar what was observed globally, as diarrhoea is said to be the second most common cause of death (UNICEF/WHO, 2009) and is the cause of admissions in developing countries (Elliot, 2010).

In the study, pre-intervention phase, managing hydration was inadequately performed, compared to the intervention phase, when the clinical practice guidelines were available. Most of the variables that were measured during the intervention phase, were followed by the prescribers accordingly. The managing AGE improved during the intervention phase and resulted in no child dying from dehydration compared to the pre-intervention phase, where deaths were observed in children with AGE, without SAM as a comorbidity. Gupta (2014), indicated that diarrhoea dehydrates the body and weakness that body immune system, which may cause malnutrition and enhances their body susceptibility to infections. Elliot (2010), alluded that optimal management with fluids minimise the risk of dehydration and its adverse outcomes. The clinical practice guidelines that were out in-place, encourage using rehydration in managing AGE, particularly using oral rehydration. Improved health outcomes, amongst them reduced death, through adherence to prescribed guidelines was appraised by (Grimshaw JM, 1993; Perlstein *et al.*, 2000; Walker, 1998).

- **Classification of dehydration**

In the intervention phase, dehydration was classified accordingly (severe, moderate, mild) and if there was no dehydration, the prescribers mentioned it as part of the diagnosis (*i.e. AGE with severe dehydration*). A

statistically significant difference was observed between the two phases of the study, improving from the (30%) observed in the pre-intervention phase to (70.8%) in the intervention phase. The importance of assessing hydration in gastroenteritis is important, to determine the immediate managing the dehydration, as indicated by Elliot (2010).

The researcher observed that most cases where the dehydration was not mentioned, were the cases where there was no dehydration observed. The prescribers were not keen in mentioning that there was no dehydration observed in the patients file. The researcher also noted that those cases were only prescribed the ORS. Surprisingly, children with no dehydration mild dehydration, in some instances with no presence of comorbidities were hospitalised, which is not supported by Elliot (2010).

These results are in-line with the results obtained by Weru (2014), who reported that approximately a third (31.1%) of the patients were not classified using terms consistent with the Kenyan MOH's paediatric protocols. This is also comparable to a study conducted in a tertiary hospital in Kenya where 19.74% of the patients admitted with acute diarrhoea had no dehydration classification consistent with the clinical practice guidelines. This may be attributable to a lack of crucial performance indicators of prescribers' initiation from management.

- **Method of rehydration appropriate**

An improvement in the appropriateness in the rehydration method was observed. During the intervention phase, (93%) of patients were rehydrated with the correct method. The researcher observed that prescribers adhered to the hydration protocol on severely dehydrated patients. All the patients who were severely hydrated were treated with boluses of fluid received rehydration through short-term infusion during the intervention. A statistically significant difference (<0.01) between the numbers of patients who were managed with fluid boluses in the pre-intervention phase and during the intervention phase. In the pre-intervention phase, there were no patients treated with boluses, despite 13 patients that had been described as being severely dehydrated. Some of the severely dehydrated patients received rehydration through short-term infusion.

Our study revealed that, despite the increasing evidence supporting the safety and efficacy of ORS, they remain underutilised as a sole rehydration method for managing acute gastroenteritis at our hospital. Common management errors including using ORS in children with little or no dehydration, administering intravenous rehydration therapy to children with only moderate dehydration and inappropriately withholding ORS or other feeding in children with vomiting were observed in the intervention phase. Although, underutilisation of ORS was observed in the study, an improved use of the ORS was observed during the intervention phase. The prescribers motivated the caregivers to give the patients ORS despite the concurrent use with the short-term infusion. These results are consistent with the results obtained by Weru (2014), where twelve (19.7%) of patients with a diagnosis of severe dehydration did not receive intravenous fluids.

A mismanagement in the method of dehydration was observed in the pre-intervention phase in some patients that were diagnosed with some dehydration. Some patients diagnosed with some dehydration without vomiting were prescribed IV therapy in the pre-intervention phase, but a major improvement was observed during the intervention where IV fluid therapy was only provided to vomiting patients. It was also of note that during the pre-intervention phase, patients without dehydration were not provided ORS at all, whilst the hydration protocol stipulates that even when there is no clinically detectable dehydration, ORS should be provided.

- **Appropriate fluid used**

During the intervention phase, there was an improvement in the correct fluid used, from (57%) in the pre-intervention phase to (95%) during the intervention phase. The plasma glucose level was important to determine the correct fluid for rehydration in the study. It was observed that in the pre-intervention, most patients received half strength of Darrows, dextrose despite their plasma glucose levels. The same observations in the pre-intervention phase were observed in patients when bolus fluid was due, there were cases where prescribers prescribed ringers lactate instead of sodium chloride.

- **Correct rate and volume of fluid used**

An improvement in the correct rate and volume of fluid was observed during the intervention phase. Most patients (97%) were provided the correct rate and volume of the IV fluid therapy compared to the pre-

intervention phase where only (57%) of the patients were provided the correct rate and volume. The challenge in the adherence in the pre-intervention phase in this variable might be attributed to prescriber's unawareness on how to calculate the rate and the volume, as the AGE was unavailable during the pre-intervention phase. This was observed during developing the guideline when there were misunderstandings and differences indicated on how the calculations are conducted. During the pre-intervention phase, the prescribers wrote the method and name of the fluid without specifying the rate and the volume of the fluid. This was a challenge as it can possibly cause fluid overload.

- **Investigations conducted appropriately**

Although, supplementary laboratory studies, including serum electrolytes to assess patients with acute diarrhoea usually are unnecessary (Teach, Yates & Feld, 1997; Nager & Wang, 2002; Elliot, 2010) however our guidelines serum electrolytes in some instances, as alluded by Elliot (2010). There were (52.86%) laboratory investigations that were conducted appropriately in the pre-intervention phase, which improved to (77.78%) during the intervention phase.

Although stool cultures are indicated in cases of dysentery but are not usually indicated in acute watery diarrhoea for the immune-competent patient (King *et al.*, 2003). Certain laboratory studies might be important when the underlying diagnosis is unclear or when diagnoses other than acute gastroenteritis is possible. Important investigations that were conducted included plasma glucose level, which was measured when the patients were provided the IV fluid therapy, to determine the correct fluid to be administered. The other relevant investigation important in the study was the kidney function tests especially in cases of severely dehydrated patients. The chemistry tests were also measured to ensure that the acceptable level of salts is maintained during the dehydration status of the patients. Prescribers ordered the relevant laboratory investigations, but the research observed that the nurses and the laboratory department were not availing the results to the prescriber for further diagnosis and treatment management. There were instances where laboratory order requested never came back to the wards would come after the patient is discharged.

- **Routine medication**

Most of the patients with acute watery diarrhoea in the intervention phase (88.10%), were prescribed the appropriate routine medication, which was zinc sulphate at the correct dose and duration compared to the

pre-intervention phase, in which only 50 (60.98%) patients were prescribed the appropriate medication. The results of the intervention phase are comparable to the results observed by Weru (2014) in his study where 92% of patients (345/376) were provided with appropriate routine medication for diarrhoea. The zinc sulphate was available throughout the duration of the study and patients received the routine medication as prescribed.

5.12 Conclusion: Compliance with the acute gastroenteritis accompanied by the hydration protocol

The intervention phase demonstrated moderate to high adherence to the clinical guidelines for managing acute diarrhoea in children under five years at RFM Hospital, ESwatini. Despite the good adherence observed, treatment practices are still improper at RFM Hospital and there is a room for improvements. The prescribers are commanded for not using anti-diarrhoeal and antiemetic drugs as they have no therapeutic value in children with AGE, as several authors their use (Elliot, 2010).

There was an improved managing dehydration in patients who presented with AGE during the intervention compared to the pre-intervention phase. An increase in the proper classification of dehydration during the intervention phase was observed compared to the pre-intervention phase and an improvement in all aspects of managing dehydration was observed. There was improved use of oral rehydration fluid therapy during the intervention phase compared to the pre-intervention phase, but for proper, adequate and frequent use of ORS, the mother of the child is the crucial person. Her knowledge, practices and attitude are of immense importance. A major public health concern is using antibiotics in treating AGE accompanied by dehydration especially in the absence of comorbidities. The findings of the study will contribute to the understanding of the most current managing childhood diarrhoea and identify the divergences justifying the need to develop alternative approach to continue reducing the impact of diarrhoea and improve the management and treatment of AGE in children.

It is evident that rehydration improves the success of clinical outcomes and compliance of ORT, decreases the rate of intravenous therapy and improves the dehydration status of the patient efficiently and decrease the rate and duration of hospitalisation. Even though there is no formal economic study, judging from the excessive cost of hospitalisation and the decreasing cost of the medication, it is likely that immediate use of ORS and use of IV therapy when necessary can reduce the health care costs in patients presenting with acute

gastroenteritis. Prescribers and nurses are aware of the importance of ORS and the positive function in acute gastroenteritis. They do not follow optimum recommendations from nutrition, laboratory examinations and drug prescriptions. Consequently, this poses significant financial losses and economic burden.

5.13 Recommendations; compliance with the acute gastroenteritis accompanied by the hydration protocol

A much more detailed prescription sheet should be designed to provide for information to be presented by the prescriber to ensure proper informed diagnosis. The prescribing sheet should include a detailed history and clearly describe the severity of the dehydration status of the patient. The cause of diarrhoea should be determined before treatment is begun and specific therapy be chosen for each of the causes. There should be a study to evaluate parents/caregivers' satisfaction on the success of ORT so that patients can be managed at home; which is more comfortable for both the patients and parents.

5.14 Severe acute malnutrition guideline

This section discusses the crucial findings about compliance with the SAM guideline during the intervention phase and also discusses findings on managing SAM during the intervention phase. The researcher looked into the impact of the SAM guidelines and compared managing SAM in the pre-intervention phase and during the intervention. Managing SAM is important when managing patients with AGE, as children with deficient malnutrition is at risk of complications (Elliot, 2010). Gupta (2014), also indicated an association between diarrhoea and malnutrition, thus substantiating the presence study in putting in-place SAM guideline in the management and treatment of AGE. In the current study, SAM was the most common comorbidity in all the phases of the study, accounting for 38.6% of comorbidities in the study. The observation of diarrhoea and SAM was documented by several authors, namely (Brown, 2003; Rice, 2000; Ochea *et al.*, 2011; Ferdous *et al.*, 2013; Gupta, 2014). The link between diarrhoea and malnutrition was observed in our study. In both the pre- intervention and intervention phases, malnutrition was the most observed comorbidity and all deaths that were observed during the intervention phase were in patients with malnutrition as a comorbidity. This observation is consistent with Rice (2000).

Appropriate managing patients with SAM following the 10 steps that were incorporated resulted in substantial improvement in morbidity and mortality in children during the intervention phase. The patients included in the intervention phase had a higher prevalence of SAM with dehydration and oedema at admission, compared to patient with SAM and dehydration without oedema. An interesting observation was that all the patients admitted with SAM during the intervention presented with diarrhoea. These factors (diarrhoea with severe dehydration and oedema) were established to increase their risk of mortality during subsequent treatment at the ward as markers of hyponatraemia, hypokalaemia or high creatinine were more common in fatal cases and increased the risk of death. Bacteraemia detected by the kidney function tests was also a major risk factor for death in those admitted with diarrhoea. For children admitted with SAM and diarrhoea there was no difference of dying associated with HIV status amongst those tested? Deficiencies in adherence to the SAM guideline were observed in some areas during the intervention phase, namely the treatment and prevention of hypoglycaemia and checking for the presence of infections during the intervention phase.

The SAM guideline recommendations are consistent with (Mbugua, 2015; Bruzzese, Giannattasio & Guarino, 2018), where they mentioned that all acute severely malnourished children should be treated with antibiotic upon admission, regardless of whether they have clinical signs and symptoms of systemic infection or not. Rice (2000) has furthermore emphasised the well-known synergistic relationship between malnutrition and infection and nutritional interventions have thus been recognised as an important approach for reducing mortality from diarrhoea. In the current study, all SAM patients (100%) were treated with broad-spectrum antibiotics as recommended in the guidelines and this practice is in-line with other studies and reviews (Rice, 2000; Nzioki *et al.*, 2008, Mbugua, 2015; Bruzzese, Giannattasio & Guarino, 2018), in which SAM patients were provided broad-spectrum antibiotics.

During the intervention phase there were 27 children admitted with SAM as comorbidity to AGE resulting in 14 deaths (51.8%). This finding is comparable to the findings of a study by Benyera (2013), which was conducted in a referral hospital in Mbabane, ESwatini and in which 111 (40.1%) of 277 children passed away in hospital, under the care of SAM clinical guidelines. Benyera (2013) concluded that case fatality rates for childhood malnutrition remain high in MGH in ESwatini, despite implementing the WHO treatment guidelines.

Step 1: Treatment and prevention of hypoglycaemia

During the intervention phase plasma glucose level were determined for most patients during admission. This was retrieved from the nurse's sheet. It was observed during the intervention phase, that nurses did not document the plasma glucose level when it was normal. There was, however, an improvement in the plasma glucose testing in the intervention phase compared to the pre-intervention phase. A guideline adherence during the intervention phase was observed. There was an improvement in the determining of plasma glucose levels (from 82% pre-intervention, to 100% during intervention). No p-value was calculated. The current study results are better compared with two Kenyan studies, in which only 29.9% of the patients were tested for random blood sugar levels Nzioki *et al.* (2008) and 16.7% Mbugua (2015), respectively.

It was furthermore encouraging to note that during the intervention phase that all hypoglycaemic patients were provided the correct fluids for hydration. The hospital had challenges with the inconsistent availability of plasma glucose strips as the hospital is a parastatal and receives most of its laboratory commodities from the National laboratory, but the plasma glucose machines used by RFM Hospital are not the same as those used by the other government hospitals which forces the hospital to buy plasma glucose strips with the limited budget the institution has.

Step 2: Treatment and prevention of hypothermia

The average temperature of patients admitted to the wards was 38.0 °C in the pre-intervention phase and 37.8 °C average temperature of in the intervention phase. There were a few patients (3/27, 11.11%), who presented with body temperatures of less than 35°C and were considered hypothermic. Although the current guidelines prescribe the necessity of availing heaters and warm blankets for patients, the RFM children's ward does not have those. Other studies do reveal a small percentage of patients presenting with hypothermia, but nursing staff fail to adhere to the guidelines of keeping the patients warm (Warfa *et al.*, 2014; Mbugua, 2015). The need of procuring the hypothermia blankets and or heaters for the children' ward is important.

Step 3: Treat or prevent dehydration

Taking into consideration that in the current study, only patients who presented with AGE as a primary diagnosis and then assessed for SAM were enrolled in the study. Those patients who did not present diarrhoea, were excluded from the study. Treating and preventing of dehydration is important in managing SAM especially with patients with oedema. Assessment of hydration status and appropriate rehydration demonstrated that a total of 27 patients (63.64%) were appropriately rehydrated in the intervention phase. A statistically significant difference between the two phases of the status concerning rehydration was observed.

The change in prescribers' managing SAM during the intervention phase may be attributed to the availability of the SAM guidelines and the associated monitoring of AGE and SAM during the intervention phase. The interaction between the research and the clinical team during this phase of the study improved hydration management as the research was able explain the importance of managing hydration and the emphasising using the correct rehydration fluid in SAM patients. During the intervention phase ward rounds, the most difficult assessment was to differentiate between oedema and a well-hydrated patient. One of challenges associated with treating oedema, SAM and severe dehydration in patients with AGE is using intravenous rehydration versus ORS. In most cases patients with AGE will be vomiting and then a Nasogastric (NG) tube has to be used. During the intervention phase, most of the needed medication, intravenous fluids and medical supplies were available, which made implementing the guideline possible.

The managing patients with shock, severe dehydration and SAM with oedema proved challenging during the intervention phase as the ward doctors and the nursing staff had difficulty in treating the dehydration during shock. The managing shock in children with severe malnutrition remains controversial (Obonyo & Maitland, 2014). Current WHO guidelines for treating children with severe malnutrition reserve intravenous fluids for those with decompensated (hypotensive) shock, advocating hypo-osmotic solutions and limiting fluid volumes, attributable to concerns about the risk of precipitating heart failure in children with severe malnutrition (WHO, 2000). For both non-malnourished and severely malnourished children the guidelines do not distinguish treating hypovolemic shock, secondary to dehydrating diarrhoea or septic shock (Obonyo & Maitland, 2014).

During the intervention phase the treatment and prevention of dehydration was adequately monitored and correctly recorded (including relevant vital signs) in all patients on ReSoMal or IV fluids to check for over-hydration and thereby decreasing the risk of cardiac failure. Only five patients (38.46%) of patients with dehydration were not appropriately rehydrated, attributable to nurses failing to adhere to doctors' orders. During the pre-intervention phase, eight patients (61.54%) were inappropriately treated for dehydration receiving IV fluids although they were not clinically shocked.

Step 4: Correction of electrolyte imbalance

All patients admitted with SAM as a comorbidity to AGE during the current study were investigated for electrolyte imbalance and 21 patients (47.73%) of the 44 patients were supplemented with potassium or provided F75. Twenty of these patients (95.24%), who had their electrolytes corrected, were in the intervention phase, compared to only one patient (4.76%) in the pre-intervention phase.

Children presenting with SAM often have a serious electrolyte imbalance which may be apparent at any time during treatment Mbugua (2015). Although the SAM guideline mentioned the importance of the chemistry baseline and follow-up results, it was observed that the follow-up chemistry was not consistently conducted in all patients, especially those that were responding well clinically. It was also noted that children who were re-admitted for the SAM were provided more care compared to those who were presenting with the condition for the first time. Treatment of electrolyte imbalance includes using F75, which contains macro- and micronutrients in quantities adequate to correct the imbalance. During the intervention phase there was a period during which F75 was unavailable in the country, but the research managed to report the F75 out of stock and the Nutrition Council in collaboration with the MOH assisted the institution with the F75.

Mbugua (2015) reported a study conducted in Pakistan, in which 93 (63.3%) of children were investigated for electrolyte imbalance, whereas Younas *et al* (2012) reported a study in which only five (5.2%) patients with SAM were investigated for electrolytes and only three patients (3.1%) were supplemented with potassium. In both phases of the study, most patients (88.64%) were appropriately treated with F75 without supplementation of magnesium, as some patients presented with oedema. This indicates an improved utilisation of guidelines when compared to Kenyatta National Hospital where approximately 56 (55%) of patients were provided commercially prepared F75 (Nzioki *et al.*, 2008).

Step 5: Treat or prevent infections

During the intervention phase, all the patients were provided treatment for presumed bacterial infection, in accordance with the SAM guideline and in accordance to Bruzzese, Giannattasio & Guarino (2018). Gentamycin and Metronidazole were initially prescribed for several patients on admission in the pre-intervention phase, although the number of patients were not quantified, but during the intervention phase antibiotics were changed to Ceftriaxone in accordance with the SAM guideline and Bruzzese, Giannattasio & Guarino (2018), where broad-spectrum antibiotics are indicated, but the author alluded that there is little evidence of efficacy in using broad-spectrum antibiotics in the absence of overt infection in malnutrition. Ceftriaxone was prescribed as a first-line treatment for all SAM patients. The ASP core team preferred using Ceftriaxone as it covers both the gram-positive and gram-negative bacteria whereas gentamycin only covers the gram-negative bacteria, has a low therapeutics index and is nephrotoxic. Confirmation of kidney infection was observed in all the patients for whom kidney function tests were performed during the intervention phase, where other patients indicated severe kidney infections compared to other patients. Patients who indicated serious infection were provided the maximum Ceftriaxone dose.

Step 6: Correct micronutrient deficiencies

A large proportion of patients with SAM (88.89%) were provided micronutrient supplements during the intervention phase compared to the (11.11%) patients in the pre-intervention phase. The patients received F75 or F100 and the nurses provided the nutritional feeds following the prescribed SAM guidelines and consequently all patients with a slight deficiency of vitamin A were received vitamin A supplementation. The prescribers and or the nurses requested the child care card from the caregiver to confirm if the child has not recently been provided vitamin A.

Some patients were provided zinc supplementation in combination with the F75 according to the SAM guideline used by the facility, which is contrary to WHO guidelines, which state that zinc supplements should not be used when these feeds are available. These disparities in using vitamin A and zinc at our hospital may be attributed to the fact that the hospital in the past had irregular supplies of F75/F100 and prescribers might be enticed to prescribe those supplements with the history of deficient supply in mind.

F75 and F100 combined with a mineral vitamin mixture (CMV) provides an adequate amount of vitamin A to manage mild vitamin A deficiency and to replace low liver stores of vitamin A during treatment (Mbugua, 2015). Higher doses of vitamin A should, however, be administered to patients who have signs of severe deficiency.

Step 7: Initiating nutritional feeds

In total 39 SAM patients, (88.64%) were prescribed the nutritional feeds, 25 SAM patients (64.10%) were in the intervention phase and 14 SAM patients (35.90%) in the pre-intervention. All 39 SAM patients received the correct amount of F75 and at the right frequency as per the SAM guideline. The feeds were monitored daily for the 39 SAM patients (88.64%). The route of feeding was specified as oral for patients who were not in shock and NGT tube for patients in shock, respectively.

Step 8: Catch-up growth and follow-up

From the 39 SAM patients who received F75, 30 SAM patients were appropriately transitioned from F75 to F100 at the correct prescribed volume and had an appropriate follow-up for monitoring thereof. During the intervention phase, 23 SAM patients (76.67%) planned follow-up, compared to only seven SAM patients (23.33%) with a planned follow-up in the pre-intervention phase and this difference was statistically significant ($P < 0.001$). Based on the above findings, there was thus a significant improvement in the follow-up during the ASP in the children's ward of RFM Hospital.

5.15 Conclusion: Compliance with the severe acute malnutrition clinical practice guideline

Treatment outcome of SAM in this study was not good, especially when the diarrhoea with hydration was also present. It indicates that over half of the patients were not cured. Guidelines for managing SAM were adequately utilised at the RFM Hospital during the stewardship programme, although it did not decrease the case fatality rates for childhood malnutrition according to the WHO standards at RFM Hospital. Some nurses in the children ward were not adequately trained in managing severe acute malnutrition at RFM Hospital and there is an elevated staff turnover which is a burden to the hospital as each nurse joining the ward need training for SAM. During the stewardship, training for prescribers and nursing sisters was conducted. The

severity of malnutrition was associated with the age of the participants, as there was a significantly higher proportion of children with amongst 6 to 12 months compared to those aged 12 to 59 months.

5.16 Recommendation: Compliance with the severe acute malnutrition clinical practice guidelines

To improve treatment outcome for children with SAM, continuous supervision has to be conducted for all healthcare professionals to avoid irrational provision of routine medication and attention should be provided for improving the capacity of healthcare professionals on proper managing SAM. This comorbid disease, they have to be treated appropriately to increase cure rate. Constant medical education for all health workers on case-managing SAM is recommended and the Pharmacy department should maintain a reliable supply of commodities needed for managing SAM. A narrower study should be conducted to evaluate the effectiveness of utilisation of guidelines for managing SAM.

5.17 Knowledge, attitudes and practices of healthcare professionals before and after the intervention

5.18 Demographic characteristics of the participants before and after the intervention

The KAP of healthcare professionals (doctors, pharmacists & pharmacy technicians, nurses and laboratory technicians) related to antibiotic use and antibiotic resistance was evaluated and compared before and after the intervention phase. The four groups of healthcare professional's background indicated a statistically significant difference, where the pharmacists/pharmacy personnel had the greatest number of participants in the study. The Pharmacy technicians' posts were filled during the intervention phase and the newly appointed Pharmacy technicians only answered the questionnaire after the intervention phase

The gender and the educational background indicated no statistically significant difference, with males having the most participants in the study. Most of the participant's highest level of education was a diploma and only a few (2) participants has a master's degree.

5.19 Knowledge, attitude and practice of health care professionals from various professional backgrounds before the intervention

The results of the survey conducted before the intervention phase, indicated no statistically significant difference between the four different groups of healthcare professionals' KAP related to antibiotics use and antimicrobial resistance. The only significant difference was observed in the knowledge (multiple-choice) and medical doctors were more knowledgeable on antibiotic use and antimicrobial resistance. The researcher expected doctors and pharmacists to be more knowledgeable on the subject compared to the other cadres because these two professionals are crucial in the management and treatment of ID. The questions that were in the questionnaire were not clinical, there were more on public health issues and doctors from RFM Hospital have not conducted research and there are not aware of public health issues.

Pharmacy personnel (pharmacists and Pharmacy technicians) and laboratory technicians were leading the QIP on antimicrobial resistance surveillance conducted over six months in the hospital. There were lot of issues that were raised in the DTC concerning antibiotics use and resistance in the hospital and the two latter professionals were the engineers of the project. The pharmacists are the custodians of antibiotics; therefore, they are expected to be more knowledgeable over any other healthcare cadre. In the current study, the pharmacists were combined with the Pharmacy technicians, therefore the results are not a true presentation of the pharmacist's opinion. In future research, pharmacists will be segregated from Pharmacy technician to get the true reflection of their opinions.

In the current study, in the pre-intervention phase, the laboratory technicians were at 20% knowledge on antibiotics use and antimicrobial resistance in the multiple-choice knowledge section. These results were expected as laboratory technicians are not involved in antimicrobial use public health. The hospital only involves the laboratory in availing laboratory results and there is no analysis conducted thereof. The researcher, then educated the laboratory technicians on issues of antibiotics use and antimicrobial resistance.

5.20 Knowledge, Attitude and Practice of Health Care Professionals from various professional backgrounds after the intervention

During the intervention phase, a statistically significant difference was observed between the four healthcare professionals. The laboratory technician had a better knowledge compared to the other healthcare professionals. There are several factors that might have contributed in the laboratory technicians to be more knowledgeable in the intervention phase. During the study, there were three new laboratory technicians that were fresh from university, therefore they studied the public health issues around antibiotics use and antimicrobial resistance. The researcher was having a frequent contact session with the laboratory staff on the issues around the problem study of the research and interventions that was put in-place to curb the inappropriate use and antimicrobial resistance.

The laboratory department is a small department and it is easy to co-ordinate/collect them and explain on issues on antimicrobial resistance. The doctors improved their attitude towards antimicrobial resistance during the intervention and laboratory technicians' good attitude decreased. The improved attitude in the doctors were caused by the positive outcomes of the antibiotic's stewardship programme. Another factor could be that the doctors were the only healthcare professionals that maintained the same doctors from the pre-intervention phase. The doctors also improved in the KAP on antibiotics use and antimicrobial resistance.

- **Knowledge, attitude and practice of healthcare professionals before and after the intervention**

The mean score on the knowledge questions (4.84) in the pre-intervention phase are comparable to the result from the similar survey conducted in DR Congo (Thriemer *et al.*, 2013). The low mean score was in large part, attributable to the three questions with flawed replies. The questions concern AB use in URTI, cross-resistance of MRSA to beta-lactam and AB dose reduction in renal failure. These question replies were also flawed in the survey conducted in DR Congo (Thriemer *et al.*, 2013). Taking cognisance of the high proportion of incorrect answer concerning URTI, this topic on the inappropriate use of antibiotics was of target during the intervention phase of the study. Most of the respondents did not know about the cross-resistance of MRSA to beta-lactam AB. The reason for the outcome could be explained by the non-functionality of microbiological facilities at RFM, disqualifying estimates of MRSA incidence. There was

insufficient knowledge about local AB resistance rates in the facility. The laboratory and the Pharmacy department answered the local AB resistance rates better than doctors and nurses.

In the current study, implementing the ASP improved the knowledge in the health care professionals especially in the questions that were improperly answered in the intervention phase. The improvement in this question was expected especially between the doctors and nurses as the research did a lot of informal education on when to decrease dose and the factors that were considered when altering a dose. The third question that improved during the intervention phase was, "Methicillin resistant - *Staphylococcus aureus* is susceptible to"? ($P=0.004$), (Table 4.11). This question was deliberated during the intervention phase especially with the laboratory department and during our ASC meetings. Most of the questions were not answered satisfactorily in the pre-intervention phase and an improvement was observed in the intervention phase.

The Likert scale questions were satisfactorily answered in both phases of the study, but an improvement was observed during the intervention phase. The difference in the outcome in the knowledge between the multiple-choice and the Likert scale was observed, which suggests that education can improve knowledge of healthcare professionals and the multiple-choice indicated a gap in knowledge on antibiotics use and antimicrobial resistance. There were questions in the intervention phase in the Likert scale that were 100% answered correctly.

The KAP-surveys provided the insights in the driving forces of antibiotics use and are corresponding to surveillance of AB resistance and AB consumption which together establish baseline information to design interventions about AB prescribing. This is the first known study to be conducted in the Manzini region and probably in the Kingdom of ESwatini to systematically demonstrate knowledge, attitudes and practice towards antibiotic use amongst healthcare professionals. These findings would be the first step in providing a baseline quantitative data of patterns of antibiotics use, knowledge and attitudes regarding antibiotics amongst healthcare professionals in this hospital. This will aid in the assessment of the adequacy of the present continuous medical educational meeting that happens every Friday in the hospital on therapeutics and provide further insight in designing future multifaceted interventions targeting specific areas to promote rational antibiotic use and replenish the knowledge and attitude divergences as an effort against antibiotic resistance.

High rates of antibiotic prescribing were identified by the present study. This high rate of prescribing could partly be explained by the respondents thinking that antibiotics does cure virus and that antibiotics will speed up the recovery of colds and flu. The baseline survey also identifies using antibiotics in acute diarrhoea and this could be partly explained by the most respondents who believed that antibiotics should be used to cure acute diarrhoea and that it shortness the duration of diarrhoea. The inappropriate use of antibiotics by doctors was revealed by the practice determined by all the healthcare professional in the baseline survey, where majority of the respondents agreed that doctors prescribe antibiotics for fever and coughing and that doctors do not do due diligence in prescribing antibiotics.

The baseline survey also revealed that managing diarrhoea from acute to chronic is not well understood. This was explained by the latter sentence and the incorrect answers obtained from the question that asked if gentamycin was indicated for chronic diarrhoea. The survey baseline also indicated that the knowledge about antimicrobial resistance is limited. This was evident when the survey revealed that most respondents were not in agreement that antimicrobials resistance is a global challenge and they did not associate using antibiotics in animals and increased resistance thereof. Surprisingly, the respondents in the baseline it and disagreement that doctors often take time to consider carefully whether antibiotics are needed or not.

The study revealed that pharmacist do not give patient education on antibiotics use, but the respondents believed that the pharmacist dispensed the antibiotics correctly with a proper advice and ensured the correct dose. Interestingly, the doctors trusted pharmacists that they will dispense the antibiotics as prescribed and conversely the healthcare professionals did not trust the doctor's antibiotics prescriptions.

The study baseline survey revealed that the healthcare professionals have a good attitude towards rational use of antibiotics and have a positive attitude towards initiation of programmes to combat the irrational use of antibiotics and the alarming rates of antimicrobial resistance. This was evident in the respondent's agreement that it is necessary to get more education about antibiotics and that there is a need to establish a course on 'rational use of antibiotics' at university level and the necessity to conduct evidence base research on antibiotics use. It was of the research surprise that the respondents established the need to formulate an antimicrobial stewardship committee in the hospital and the necessity to have continuous profession education about antibiotics.

From the present survey, potential fields of intervention are the following: improvement of knowledge about AB properties and usage targeting medical students during their university curriculum, the provision of unbiased and evidence-based information about AB and local AB resistance rates to all prescribers and implementing quality assurance for drugs to improve confidence amongst the general public and professionals. Educational measures such as trainings are highly welcomed and implementing AB committees should be studied at national pilot settings.

The significant association between overuse of antibiotics and antibiotic knowledge suggests that educational campaigns that emphasise knowledge may be effective to inverse the inappropriate use of antibiotics. This finding is crucial in developing comprehensive and multifaceted interventions. Respondents' inadequate knowledge of antibiotics was identified to not correlate positively with attitude, therefore, in this baseline survey, inappropriate knowledge of antibiotics was identified to be a predictor for negative practice towards antibiotic use.

KAP-surveys however have characteristic limitations: respondents may be elicited to the topic and this - in combination with the multiple-choice format of the questionnaire - may direct them to socially desirable answers. Respondents with no interest in the topic in question can just answer to fill the survey but not a true reflection of the respondents especially respondents in a remote and busy health centres. The completion of the questionnaire anonymously and assurance of confidentiality provided to the respondents would minimise the over- and under-reporting. This survey has a strength of addressing medical doctors, pharmacists, Pharmacy technicians, nurses and laboratory technicians. The researcher could not find any comparable study with conducted a study on KAP towards antibiotics use and antimicrobial resistance on the four healthcare professionals, but studies were conducted on medical doctors, students and the public. A further strength is the intervention phase data that represented that reflected the changes in respondents' knowledge and attitude after the ASP intervention in relation to antibiotics use.

To inverse these limitations, the present survey was adopted from Thriemer *et al.* (2013), which have validated by a team of local professionals and took into account limitation in time and concentration of the respondents. The present study emphasised on the KAP of medical doctors, pharmacists, Pharmacy technicians, nurses and laboratory technology in an elevated volume, resource-limited setting in the Kingdom of ESwatini. To fully understand the whole extent of inappropriate AB prescribing and usage, further research

is needed amongst the other aspects of interventions that can be used to curb inappropriate use of AB for example, the importance of ASP and knowing the perceptions of healthcare professionals towards the ASP's in healthcare professionals. The KAP can also be conducted in all other healthcare facilities in the country. Differences between the results of other health facilities may advise for interventions to address the national challenge of antibiotic resistance. Despite these limitations, the present findings provide valuable information for evaluating and improving knowledge, attitude and practice towards antibiotics use.

5.21 Conclusion

Differences in perspective exist between the four groups of health care professionals regarding the various aspects of antibiotic use and antibiotic resistance. The development and implementing the ASP improved the KAP of all the health care professionals. The present findings allow for important relative work with existing (although might be limited) and future investigations at RFM Hospital and in the Kingdom of ESwatini. Given the rapid growth rate of antibiotic resistance at RFM Hospital and recognised health issues related to inappropriate use of antibiotics, the present findings emphasise important concerns regarding antibiotics amongst healthcare professionals at RFM Hospital. The crucial findings of this study will assist the DTC at RFM Hospital to plan and establish future effective multifaceted interventions to improve the appropriate use of antibiotics.

5.22 Recommendations

Qualitative and quantitative studies need to be conducted at institutional, regional and national level to identify the determinants of attitudes, behaviour, expectations and motivation that lead people to use and misuse antibiotics. Healthcare institutions should improve communication about antibiotic appropriateness between healthcare professionals and patients.

The Swazi Government should support and commit to investing in public health education programmes for both public and healthcare professionals, including policymakers, doctors, nurses, pharmacists and patients. The public education programmes should be in all media meaning that should be targeted more efficiently at those who have low knowledge, negative attitude and inappropriate practice towards antibiotic use. These

campaigns should use behavioural and influencing theories and repetition to target modifications in health risk attitudes. An evaluation of its effectiveness should follow each campaign

The ESwatini government should require its healthcare system to urgently facilitate the proper regulations and prescribing policies and controls for antibiotics. Policies of auditing antibiotic prescriptions in the healthcare facilities and investigating the consultation behaviour and other behavioural components engaged in patients' expectations for antibiotics. Pharmacist's should be authorised the function in raising awareness in using antibiotics and antibiotic resistance, emphasising pharmacists' function in health education and promotion and responsibility in elimination antibiotic dispensing without prescription from an authorised prescriber and monitoring sources of obtaining antibiotics through enforcing the strict regulations.

Finally, public health strategies should be developed, to curb areas of misconception and misuse of antibiotics. Further research to investigate knowledge, attitude and practice towards antibiotic use amongst expatriates will assist in the adoption and implementing successful future policies to promote rational antibiotic use amongst the public in Kuwait.

5.23 Study limitations

The study was single-centred to RFM Hospital. This can lead to multiple biases, a failure to deliberate developments in antibiotic use and absence of assessments with antibiotic use in other health facilities without ASP. Using convenience sampling limited the study because to generalise conclusions about a population, a random sample, or scientifically selected subset of that population must be drawn (Rea & Parker, 2005). In the pre-intervention phase, the medical records were incomplete, leading to misclassification of the accuracy of the submitted data, the missing data comprised the minimum number of cases that were supposed to be enrolled in the study to inform better comparison between the two phases of the study. The study was accomplished over a limited period.

In the current study, antibiotics use intervention was only based on all children that were diagnosed with AGE as a primary diagnosis, this meant that the ASP core team was unable to triage other complex cases which needed robust interventions, which should assist to avoid overestimation of the intervention effects.

We excluded children admitted in ICU from our intervention as these patients might receive the most restricted antibiotics. This special population is especially vulnerable to infections and the empiric therapy for them may tend to be broader spectrum antibiotics.

The study was also limited to prescribers and nurses working in the children's ward during the duration of the study and excluded those prescribers working in other departments. The perceptions, beliefs, attitudes and practices of the health care professionals may change over time, but the findings of this study were limited to what the participants believed and perceived about antibiotic use and antibiotic resistance at the time in which participants completed the survey.

The study assumed that all health care professionals working in the paediatrics' department were aware of the guidelines provided by the research. The study assumed that the prescribers treated patient without oppression to please the research or the hospital management. The study assumed that the results produced by the laboratory microbiology were a true reflection of the microbiology results. The study assumed that research participants completed the KAP questionnaire independently and provided honest responses to the questions to the best of their knowledge and ability. It was also assumed that responses to questionnaire were based on each individual health care professional's perceptions and not based on what others might believe.

5.24 Conclusion

There is an evidence that ASPs are successful at increasing appropriate antibiotics use and limiting the development and spread of antibiotic resistance. The nature of ASP interventions and the outcomes of importance to patients can determine study design selection and methodology. Well-designed ASPs aimed at evaluating ASP impact on antibiotics use. Patient outcomes are critical for maintaining efficient, high quality patient care, promoting essential antibiotic use.

The ability to assess the effect of an ASP intervention is often limited by external factors, beyond the control of the research. Health commodities such as antibiotics shortages, availability of microbiology and chemistry reagents, high personnel turnover and expansion of services, can have a major influence on intervention outcomes. It can therefore be difficult to isolate the true effect of an intervention from these external

influences. It is also important to recognise that several ASPs do not have adequate funding to support their activities. Thus, the lack of these resources can be a major barrier to the conduct of effective evaluations of ASPs.

There is an explicit need to appraise various ASP interventions in a broad range of clinical settings from primary health care to tertiary hospitals; from general clinics to specialised clinics. Although the predominant goals of essential antibiotic prescribing are the same across various healthcare settings, the approach to supporting essential prescribing should be tailored to each setting. Interventions should for instance be customised concerning age (children vs adults), or conditions (acute infections vs chronic infections).

The conduct of methodologically comprehensive evaluations of ASP interventions can inform best practice and policy. The findings of several recent studies (Pate *et al.*, 2012; Cairns *et al.*, 2013; Cisneros *et al.*, 2013, Mendelson *et al.*, 2016; Brink *et al.*, 2013 and Boyles *et al.*, 2016) have indicated the positive impact that ASPs can have on antimicrobial resistance and patient outcomes; however, more work is needed to further inform the field by identifying effective and efficient stewardship interventions. To identify the most effective interventions and implementation strategies, studies evaluating ASP interventions should be essentially planned and directed to minimise bias and maximise internal validity. Continued effort is needed to indicate the value of ASPs to increase the evidence base that informs best practices for stewardship in all healthcare settings.

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RALEIGH FITKIN MEMORIAL HOSPITAL

To : Hospital Administrator

From : Senior Pharmacist

Cc : Drugs and Therapeutics Committee Chairperson

Date : 1 February 2016

RE: PERMISSION TO DO A PROSPECTIVE STUDY ON CHILDREN LESS THAN 5 YEARS

I am a Senior Pharmacist working as a supervisor for the Pharmacy department and leading both the clinical and the administrative duties of the pharmacy. I am currently enrolled at Stellenbosch University as the main investigator in the research, titled:

Investigating the effect of antimicrobial interventional programmes in prescribing antibiotics in AGE and its co-infections in children less than 5 years at Raleigh Fitkin Memorial Hospital, in Swaziland

I have enclosed the proposed protocol and all its accompanying documentation. The study will formally start after an approval from Stellenbosch University Ethics Committee. This is a prospective study that will hopefully influence prescribers prescribing patterns for the benefit of the patient and the hospital at large.

Thank you.



SWAZILAND NAZARENE HEALTH INSTITUTIONS (SNHI)
RALEIGH FITKIN MEMORIAL (RFM) HOSPITAL
COMMUNITY HEALTH CLINICS



At Junction of David Hynd Road & Ligusha Street

P.O. Box 14 Manzini 200 Swaziland

12 July 2016

Stellenbosch University
The Health Research Ethics Committee
Tygerberg

Dear Ethics,

Re: S16/02/026
INVESTIGATING THE EFFECT OF INTERVENTIONAL
ANTIMICROBIAL PROGRAMMES ON THE APPROPRIATE
PRESCRIBING OF ANTIBIOTICS FOR ACUTE
GASTROENTERITIS AND IT'S CO-INFECTIONS FOR
CHILDREN LESS THAN FIVE YEARS AT RALEIGH FITKIN
MEMORIAL HOSPITAL, SWAZILAND

With reference to the correspondence from the Ethics Committee to ascertain if the antimicrobial stewardship, development and use of guideline will be a standard of care; The Drugs and Therapeutic committee (DTC) together with the management of RFM Hospital have approved the antimicrobial stewardship committee. This committee will be a subcommittee of the DTC and will do all the activities relating to antimicrobials. Their activities will be incorporated in the hospital's standard of care.

The terms of reference of the antimicrobial stewardship have been attached.

Kind Regards,

Senlour Medical Officer,
Chairperson of the Drugs and Therapeutic Committee

TELEPHONE: 2506 4000
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UNIVERSITEIT STELLENBOSCH-UNIVERSITY
JOU KENNISVENNOOT - your knowledge partner

Approval Notice Response to Modifications- (New Application)

25-Jul-2016
Matsebula-myeni, Zinhle ZC

Ethics Reference #: S16/02/026

Title: Investigating the effect of interventional programs in combating inappropriate use of antibiotics in the management and treatment of Acute Gastroenteritis in children less than 5 years at Raleigh Fitkin Memorial hospital in Swaziland

Dear Ms Zinhle Matsebula-myeni,

The **Response to Modifications - (New Application)** received on **07-Jun-2016**, was reviewed by members of **Health Research Ethics Committee 1** via Expedited review procedures on **25-Jul-2016** and was approved.
Please note the following information about your approved research protocol:

Protocol Approval Period: 25-Jul-2016 -24-Jul-2017

Please remember to use your **protocol number** (S16/02/026) on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review:

Please note a template of the progress report is obtainable on www.sun.ac.za/rds and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Translation of the consent document to the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372
Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Department of Health (healthres@pgwc.gov.za Tel: +27 21 483 9907) and Dr Helene Visser at City Health (Helene.Visser@capetown.gov.za Tel:

**Knowledge, attitude and knowledge of antibiotics use in children among
healthcare workers at the Raleigh Fitkin Memorial hospital**

SECTION A

Demographic characters

Tick in correct box ()

Age: 20-29 Sex: M F

30-39

40-49

50-59

➤ 60

Profession background: Paediatrician :

Medical doctor:

Family nurse practitioner:

Staff nurse:

Pharmacist:

Pharmacy technician:

Laboratory technologist:

Laboratory technician

Highest Education level: Diploma

Degree

Post graduate diploma

Honours

Masters

Doctor of philosophy

SECTION B

Healthcare professional's knowledge on antibiotics use					
Question	Strongly agree	Agree	Neutral	Strongly disagree	Disagree
Different antibiotics are needed to cure different diseases					
Antibiotics are effective against bacteria					
Antibiotics are effective against viruses					
Antibiotics will speed up the recovery of colds, cough					
Antibiotics should be used to acute diarrhoea					
Antibiotics shortens the duration of acute diarrhoea					
If you get side effects during a course of antibiotics treatment you should stop taking them as soon as possible					
If you get some kind of skin reaction when using antibiotics, you should not use the same antibiotic again					
Is amoxicillin sensitive to E.coli bacteria					
Is gentamycin indicated for chronic diarrhoea					

Is Metronidazole the best drug for acute diarrhoea					
Ceftriaxone is the golden treatment for treating bacterial pneumonia					
Antibiotics can cause imbalance in the body's own bacterial flora					
The unnecessary use of antibiotics can increase the resistance of bacteria to them					
Resistance of antibiotics is a world-wide problem					
The use of antibiotics amongst animals can reduce the effect of antibiotics amongst humans					
Humans can be resistance to antibiotics					

1 A 4-year-old girl has diarrhoea for 4 days (3 stools/day). She has no fever at examination nor during the last few days. Which treatment do you propose?

- a) Amoxicillin p.o.
- b) cotrimoxazole p. o.
- c) amoxicillin -clavulanic acid p.o.
- d) no antibiotic treatment, only oral rehydration

2 A 6-year-old child has a fever of 38 °C, purulent rhinitis and angina for two days. At inspection, the throat is reddish. Which treatment do you recommend?

- a) cotrimoxazole p. o.

- b) amoxicillin p.o.
- c) amoxicillin -clavulanic acid p.o.
- d) no antibiotic

3 During your ward round, you see two patients with severe renal failure. Patient A is a 4 year old suffering from serious cellulitis at the leg, she is treated with clindamycin. Patient B is a 5 years old with a juvenile diabetes which is empirically treated for septicaemia with Ceftriaxone. Dosage reduction is needed for:

- a) Patient A
- b) Patient B
- c) both patients
- d) in neither patient A nor patient B

4 Which one of the following antibiotics is safe in neonates?

- a) Amoxicillin
- b) ciprofloxacin
- c) gentamicin

5 Which one of the following antibiotics has the best activity against anaerobes?

- a) Ciprofloxacin
- b) Metronidazole
- c) cotrimoxazole

6 Methicillin-resistant - *Staphylococcus aureus* is susceptible to:

- a) amoxicillin-clavulanic acid
- b) cefotaxime
- c) Ceftriaxone
- d) none of those antibiotics

7 Which one of the following antibiotics most effectively crosses the blood-brain barrier?

- a) Clindamycin
- b) Ceftriaxone
- c) vancomycin

8 Aminoglycosides such as gentamicin are very active if they are administered as follows:

- a) orally three times daily
- b) parenteral once daily
- c) parenteral three times daily

9 At Raleigh Fitkin Memorial Hospital, what is according to your information the estimated resistance rate of Salmonella Typhi to Cotrimoxazole (Bactrim)?

- a) 0-10%
- b) 10-20%
- c) 25-50%
- d) 50-75%

10 At Raleigh Fitkin Memorial Hospital, what is according to your information the estimated resistance rate of Klebsiella to Ceftriaxone?

- a) 0-10%

b) 10-20%

c) 25-50%

d) 50-75%

SECTION C

Healthcare professionals' attitude and awareness on antibiotics use					
Questions	Strongly agree	Agree	Neutral	Strongly disagree	Disagree
There is abuse on antibiotics at present					
Antibiotics resistance has become a problem in Swaziland					
Abuse of antibiotics has become the main cause leading to bacterial resistance					
Antibiotics resistance affects the livelihood of the community					
It is necessary to get more education about antibiotics					
There is a need to establish a course on 'rational use of antibiotics' at university level					
It is necessary to carry out evidence base research on antibiotics use					
It is necessary to formulate an antimicrobial stewardship committee in the hospital					
It is necessary to have continuous profession education about antibiotics					

Section D

Healthcare professional's behaviour on using antibiotics				
Questions	Strongly Agree	Agree	Neutral	Strongly disagree
Doctors prescribe antibiotics when having fever (>38.5°C)				
Doctors prescribe antibiotics for coughing				
Doctors often tell patients/caregivers on how antibiotics works				
Pharmacists often tell patients how antibiotics should be used				
Pharmacists often ensure the right dose of antibiotic is given to the patient				
Pharmacists often give patient education on antibiotics				
Doctors often prescribe antibiotics because the patient expect it				
Doctors often consider carefully whether antibiotics are needed or not				
Pharmacists trust doctors' decisions when they prescribe antibiotics				
Doctors trust pharmacists that they will dispense and advise patients on the use of antibiotics				
Doctors advise that antibiotics can be used when cough last up to two weeks or more				
Patients can be given antibiotics when they ask them				

ANNEXURE C: PARTICIPANT CONSENT FORM

TITLE OF THE RESEARCH PROJECT:

INVESTIGATING THE EFFECT OF INTERVENTIONAL ANTIMICROBIAL PROGRAMMES ON THE APPROPRIATE PRESCRIBING OF ANTIBIOTICS FOR ACUTE GASTROENTERITIS AND ITS CO-INFECTIONS FOR CHILDREN LESS THAN FIVE YEARS AT THE RALEIGH FITKIN MEMORIAL HOSPITAL, SWAZILAND

REFERENCE NUMBER : S16/02/026

PRINCIPAL INVESTIGATOR : Zinhle Matsebula-Myeni

ADDRESS : P. O. Box 2108 Matsapha,

Fairview North, Manzini

Swaziland

CONTACT NUMBER :

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the Principal Investigator any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved.

This study has been approved by the **HREC at Stellenbosch University** and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

Study setting

The study will be conducted at Raleigh Fitkin Memorial Hospital, there will be 100 participants that will be recruited in the prospective arm.

Aims of the study

The aim of this research is to assess prescribers' antibiotics prescribing patterns; knowledge, attitudes and practices before and after an interventional antimicrobial programme, established by the principal investigator through the antimicrobial stewardship committee to achieve appropriate prescribing of antibiotics in AGE and associated co-infections. This research will also contribute to global initiatives to address and combat the inappropriate use of antimicrobials, particularly in the public sector in developing countries.

Purpose of the study

To determine the number /cases of prescribers correctly prescribing antibiotics: Optimising the duration of choice and dose of empiric therapy: antimicrobial stewardship.

To determine the implementation of the protocols for management of AGE, pneumonia, malnutrition, URTIs and otitis media, and an antibiotic policy.

To determine the improvement of prescribers' knowledge, attitude and practice.

Methodology

There will be a prospective audit of the ASP established at Raleigh Fitkin Memorial Hospital after obtaining approval by the hospital administration and support by the medical staff. The ASC with the paediatrician team will monitor the management and treatment of AGE and its co-infections, two (2) calendar days after

treatment is initiated by the clinician. The committee will use the TOR, developed by the Principal Investigator. Patients to be reviewed by the ASC will be identified by the nursing sisters in the special care unit and the children ward. The ASC will approve the new protocols on AGE, pneumonia, Otitis media, malnutrition, bronchitis and URTIs. The pharmacist will review the medical records of the patients receiving one or more antibiotics for medical history and physical findings necessitating initiation of antibiotics, including culture data, radiographic findings, and significant laboratory values, as well as dosing and intended duration. Recommendations will then be communicated to the clinician caring for the child. Interventions will be categorised by type of recommendation and the prescribing antibiotic policy which will include the following: discontinue the antibiotic; narrow or broaden antimicrobial therapy based on culture and susceptibility data; convert the administration method from parenteral to oral route; narrow or broaden empirically; increase or decrease the dose; shorten or lengthen the planned duration of therapy, consolidate to fewer antimicrobials, or obtain an ID's consult. ID's consultation will be reserved for cases with multiple complex issues and/or where the diagnosis meets the criteria for ID's consultation in the institution.

All prescriptions of children that will be diagnosed and admitted in the institution with AGE as a primary diagnosis between 1 April 2016 and 31 September 2016 will be selected. A separate prescription form will be filled for antibiotics. Using a newly developed prescription form for inpatients. The diagnosis of AGE will be confirmed either according to the International Classification of Disease and Related Health Problems, 10th revision (ICD 10) or based on the results from a rapid RV (Retroviral) diagnostic test. Medical history will be collected from the medical charts or the hospital database, and the duration of hospitalisation/ and or consultation for AGE, defined as the number of days between the date of admission and the date of discharge, will be automatically calculated in the medical chart database. A questionnaire will be completed on demographic data, diagnosis, and treatment of AGE and co-infections. Before and after the intervention are put in-place, a questionnaire designed by the researcher will be used to determine the knowledge, attitude and practices of prescribers on antibiotics at RFM Hospital.

Randomisation process

During statistical analysis, one hundred participants will be randomly selected from the participants that were in the study. Their chart numbers will be arranged from the smallest number to the largest number and the 1st hundred participants will be selected and analysed.

Why have you been invited to participate?

Your participation as a prescriber will contribute positively to the research. The study is on children less than 5 years and you are working under that children department.

What will your responsibilities be?

Diagnosing, prescribing and management of children with acute gastroenteritis and its co-infections namely pneumonia, Otitis media, malnutrition, bronchitis and upper URTIs according to the approved protocol.

Participant in the wards rounds that will include the antimicrobial stewardship committee

Will you benefit from taking part in this research?

The study will benefit you in gaining knowledge on antimicrobial stewardship and learning more on antibiotics use.

You will gain more knowledge on how to give the best optimal treatment of the five conditions namely: Acute gastroenteritis, pneumonia, Otitis Media, Bronchitis, Malnutrition and URTIs.

Gain more knowledge in procedures on culture and sensitivity

Gain insight on optimising antibiotics use

Are there in risks involved in your taking part in this research?

There are no potential risks to your participation; however, you may feel uncomfortable participating in the study. You do not have to participate. The information will not be used for appraisal purposes.

If you do not agree to take part, what alternatives do you have?

If you do not agree to participate in the study, you will continue with your own management of the patients with AGE and its co-infections.

Who will have access to your medical records?

The data will be stored in the Principal Investigators office and stored privately. The statistician will have access to the coded information of the patient. There will be no names published for public consumption. The data will be stored for a minimum of five years at Stellenbosch University in their research archives. The data will also be stored in the Principal Investigator password protected computer and in a locked cupboard file during the study. Upon completion of the data collection and data entry, all hard copies (consent documents, survey instruments, etc.) will be destroyed. The remaining data will be maintained indefinitely; however, the data may be used in future research studies of the Principal Investigator and or the supervisor. The results will not be shared with the management, to prevent victimisation.

Will you be paid to take part in this study and are there any costs involved?

There will be no costs involved for you, if you do take part.

Is there anything else that you should know or do?

You can contact the institution Research Chairperson, Dr **xxxxx**, if you have any further queries or encounter any problems.

You can contact the Principal Researcher if you have any technical queries, or anything to do with research project at **xxxx**

You can contact the HREC at **021-938 9207** if you have any concerns or complaints that have not been adequately addressed by Principal Investigator and the Research Chairperson.

You will receive a copy of this information and consent form for your own records.

Declaration by participant

By signing below, I agree to take part in a research study entitled *(INVESTIGATING THE EFFECT OF INTERVENTIONAL ANTIMICROBIAL PROGRAMMES ON THE APPROPRIATE PRESCRIBING OF ANTIBIOTICS FOR ACUTE GASTROENTERITIS AND IT'S CO-INFECTIONS FOR CHILDREN LESS THAN FIVE YEARS AT RALEIGH FITKIN MEMORIAL HOSPITAL, SWAZILAND)*

I declare that:

I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.

I have had a chance to ask questions and all my questions have been adequately answered.

I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.

I may choose to leave the study at any time and will not be penalised or prejudiced in any way.

Signed at..... on..... 2016.

Signature of participant

Signature of witness

Declaration by the investigator

I..... declare that:

I explained the information in this document to

I encouraged him/her to ask questions and took adequate time to answer them.

I am satisfied that he/she adequately understands all aspects of the research, as discussed above

I did/did not use an interpreter.

Signed at..... on..... 2016.

Signature of investigator

Signature of witness

INVESTIGATING THE EFFECT OF INTERVENTIONAL ANTIMICROBIAL PROGRAMMES ON THE APPROPRIATE PRESCRIBING OF ANTIBIOTICS FOR ACUTE GASTROENTERITIS AND IT IS CO-INFECTIONS FOR CHILDREN LESS THAN FIVE YEARS AT RALEIGH FITKIN MEMORIAL HOSPITAL, SWAZILAND

Demographics

Name _____ of _____ hospital: _____
Region:.....

1.1 PRESCRIBER'S INFORMATION:

Qualifications:

Tick in the correct box

Paediatrician Medical Doctor Family Nurse Practitioner Nurse Other

Work experience:

years 2-4 years 4-6 years 6-8 years 8-10 years > 10 years

1.2 PATEINT INFORMATION:

Age: Gender: Male Female: Weight:

Admission details: First attendance RE- attendance

Residential address

Region: Manzini; Hhohho; Shiselweni; Lubombo

1.3 CAREGIVER'S INFORMATION:

Age: <18 years: 18-25 years:25-30 years: 30-35 years: 35-40 years :>40 years

Gender: Male female:

Education background: No formal education Primary education: Secondary education: University level:

Relationship with patient: Mother; Father; Sister; Aunt; Helper

PATIENT'S HISTORY

Signs and symptoms of diarrhoea :

Temperature: _____ Capillary Refill: _____

Time elapsed between onset of diarrhoea and attending health centre in days: _____

Frequency of passing stool per day: _____

Consistency and nature of stool: _____

Complaints of patients: 1. _____ 2.
3.....

Patient level (Circle one): Level 1 Level 2 level 3

Point of admission: General OPD emergency room: Baylor clinic:

Place of admission: Special care unit children's ward ICU:

Prescriber's recommendation: admission monitored at emergency room:

2.2 Other condition at admission:

HIV: Exposed not exposed:

Pneumonia: acute malnutrition: severe malnutrition: bronchiolitis: otitis media:

Coughing: allergic rhinitis: tonsillitis:

Any other chronic condition: please
specify.....

Doctors' orders:

Laboratory (Please attach)

X-ray (Please attach)

Final prescriber's diagnosis:

2.3 Medication history (last 6 months)

Antibiotics used: 1. 2. 3.	Indication: 1. 2. 3.	Facility level: Clinic/PHU/Hospital 1. 2. 3.
Other Medication used: 1. 2. 3.	Indication: 1. 2. 3.	Facility level: Clinic/PHU/Hospital 1. 2. 3.
Chronic medication: 1. 2. 3.	Indication: 1. 2. 3.	Facility level: Clinic/PHU/Hospital 1. 2. 3.

2.5 Laboratory results

Were laboratory tests used before prescribing antibiotics: YES NO

Were antibiotics continued after laboratory results: YES NO

Culture done	Bacterium cultured	Sensitive drugs	Intermediate drug	Resistance drug
Blood				
Pus				
Urine				
Stool				
CSF				
Synovial fluid				
Vomit				

Culture done	Bacterium cultured	Sensitive drugs	Intermediate drug	Resistance drug

Are the sensitive drug available: YES NO

Which is the cheapest available drug: YES NO

Which drug was dispensed and why?.....

.....

.....

Full medication cost stay:

<p>Total cost:</p>

PLEASE ATTACH RESULTS:

INTERVENTION:

Description of intervention	Tick the relevant intervention	Any further comments
Discontinue the antibiotic		
Narrow or broaden antimicrobial therapy		
Convert from parenteral to oral route		
Narrow or broaden empirically		
Increase or decrease the dose		
shorten or lengthen the planned duration of therapy		
Consolidate to fewer antimicrobials		
Obtain an ID consult		

3.....

4.....

5.....

2.8 Symptoms on discharge

1.....

2.....

3.....

2.9 Medication on discharge

.....

.....

.....

ALIGNMENT TO antimicrobial stewardship committee

Did the prescriber align to the antimicrobial stewardship committee recommendations? Yes No Partially comply

Did the prescriber align to the Standard Treatment Guideline or Protocol? Yes No Partially Comply

Terms of reference

The antimicrobial stewardship committee

Accountability:

The antimicrobial stewardship committee (ASC) is accountable to the hospital DTC.

Purpose:

The Raleigh Fitkin Memorial Hospital (RFMH) Antimicrobial Stewardship (AMS) Committee will provide oversight and input into the development, implementation and ongoing review of the AMS programme at RFM Hospital. The AMS programme will involve a systematic approach to optimising the use of antimicrobials in RFM Hospital to improve patient outcomes, reduce inappropriate antimicrobial use, and reduce adverse consequences of antimicrobial use (including antimicrobial resistance, toxicity and unnecessary costs).

Primary objectives:

Advisory: The ASC recommends the development and adoption of professional policies regarding antimicrobial agents within RFM, including the evaluation, selection, procurement, distribution, use, safe practices, control, and clinical protocols of antimicrobials

Education: The ASC recommends the development of programmes and educational tools designed to meet the needs of AHS staff for complete and current knowledge on matters related to antimicrobials and their appropriate use.

Research: The ASC encourages and supports research on antimicrobials, antimicrobials use, and antimicrobials Pharmacoeconomics.

Secondary objectives:**1. AMS Rounds**

The antimicrobial stewardship (AMS) team will carry out AMS rounds at RFM Hospital every Friday of each week. The purpose of these rounds will be to review antimicrobial prescribing in targeted clinical areas (e.g. critical care, respiratory, and surgical wards). The AMS team is authorised to make point-of-care interventions (such as adjusting antimicrobial therapy based on allergy mismatch, microbiology results or organ dysfunction), and/or discuss their recommendations with treating teams.

2. Monitoring of Antimicrobial Usage and Resistance

The AMS program incorporates a range of data collection methodologies to monitor both the quantity and quality of antimicrobial usage and examine processes associated with antimicrobial prescribing and supply. These methods include (but are not limited to):

Analysis of Antimicrobial Utilisation Surveillance Program (NAUSP) reports for RFM every 3 months;

Analysis of carbapenem antibiotic usage at RFM every 3 months;

Review of audits of compliance with antimicrobial prescribing guidelines at RFM Hospital.

The AMS committee also works closely with the Management Sciences for Health to extract and evaluate data on local antimicrobial resistance rates and changes or trends that emerge over time. This includes:

Review of multi-resistant organism (MRO) surveillance data every 3 months in liaison with a representative from the Infection Prevention and Control Committee;

Review of cumulative hospital level antibiogram for RFM Hospital every 12 months.

The core objectives of the committee includes:

1. To develop, implement, maintain and evaluate policies, protocols, and programmes to promote safe, optimised, and cost-effective antimicrobial use.
2. To regularly collect and evaluate process and outcome measures to ensure successful antimicrobial stewardship practices.
3. To identify areas of suboptimal antimicrobial use through prospective audits, antimicrobial order forms or surveillance and recommend appropriate intervention strategies.
4. To provide regular feedback and reinforcement to prescribers regarding audit results and the appropriateness of their antimicrobial use with recommendations for improvement as necessary.

5. To develop and deliver educational programmes for RFM Health staff targeted at areas of weaknesses in antimicrobial prescribing.

6. To work collaboratively with the provisional antimicrobial stewardship Group and the national antimicrobial stewardship committee in order to align with the provincial and the national wide antimicrobial stewardship initiatives.

7. To plan action, including risk assessment, to improve the effectiveness of the AMS programme at RFM Hospital.

Organisational risks addressed by this committee:

The key risks to the organisation that will be managed by this committee include:

Risks associated with inappropriate use of antimicrobials (including antimicrobial resistance, toxicity and unnecessary costs);

Conflict that may arise from formulary restrictions and/or performance measures based on concordance with clinical guidelines.

Membership and roles

All members are expected to play an active role in the development, implementation and review of AMS strategies at RFM Hospital. Members represent their unit, department or discipline, and as such, may liaise with staff in their unit when broad input is needed e.g. development of a protocol for a specific infectious condition. Members are also expected to champion the AMS programme in their own unit, and demonstrate leadership for AMS in their prescribing practices, as well as in their knowledge and attitudes.

Membership of the AMS committee will consist of:

Senior Pharmacist (Executive Chair)

Medical Officer (Deputy Chair)

Clinical microbiologist (AMS lead)

AMS Pharmacy Technician (Secretary)

Patient Safety and Clinical Quality Manager

Nursing representatives

Medical staff representatives (paediatrician, surgery, obs and gyane, casualty)

Consumer representative

Infection Prevention Control representative

Other personnel may be co-opted as required to assist the work of the committee.

Head of AMS team

Is an ID Physician/Paediatrician, senior physician or clinician, senior pharmacist deemed to be suitable by the Hospital Director?

Represents the AMS team in the hospital infection control committee and gives feedback on AMS programme.

Co-opted into the DTC when considering changes of antimicrobials in the hospital formulary

Prepares surveillance and audit reports for submission to state and national level

Proposes annual AMS activities with the Hospital Director and various departments

Infectious disease physician or paediatrician

Leads the technical component of antimicrobial stewardship team.

Consults and advises on specific stewardship related cases and issues

Antimicrobial pharmacist or clinical pharmacists

Is preferably a dedicated full-time Pharmacist trained in AMS

Clinical role in conjunction with other members of the AMS Team

Gives technical know-how on finer aspects of antimicrobials and newer agents.

Works with and educates ward pharmacists to identify potential patients for stewardship interventions (e.g. de-escalation etc)

Ensures dose optimisation is carried out especially for complex antimicrobials and complex clinical scenarios.

Enforces the approval system of restricted antimicrobials

Ensures safe and effective use of medication to reduce risk for errors and adverse events

Surveillance of antimicrobial use

Collection and analysis of local consumption and expenditure

Provision of data to regional /national surveillance programmes

Carries out and analyses point prevalence studies on antimicrobial usage

Audit and feedback

Leads and conducts appropriate antimicrobial audits

Provides timely feedback for future improvement

Clinical microbiologist

Provision of guidance on appropriate diagnostic tests in microbiology.

Provision of timely and accurate reporting of culture and antimicrobial susceptibility data.

Ensures selective reporting of antimicrobial susceptibilities and interpretative reporting of microbiology results.

Provision of antimicrobial resistance patterns data in individual hospital on yearly basis.

Ensure the appropriateness of microbiology request, sample collection (types, time, date taken and documentation) and sample quality.

Work closely with the attending clinician, IDs specialist and antimicrobial pharmacist in the management of patients with infections

Information technology officer

Hospitals with existing IT systems may consider including an IT personnel into the AMS team to assist with :

Creating localised electronic decision-making systems that can be available through the hospital network system.

Providing AMS team access to microbiological data and antibiotic utilisation data.

Producing automated antimicrobial utilisation data and other programmed clinical data.

Infection control nurse

AMS teams frequently chance upon opportunities to tighten infection control practices during their course of the work. Having an Infection Control Nurse Practitioner within the team complements the efforts of the AMS team in bringing down resistance rates.

Meeting frequency:

Monthly

Any additional meetings will be at the discretion of the antimicrobial stewardship committee chairperson. The meetings will be set at the beginning of each calendar year and circulated to members.

Quorum

A quorum will be half the members plus one.

Agenda / minutes:

An agenda will be established prior to each meeting and distributed to committee members. Following each meeting, a "Meeting Summary" will be distributed outlining action items and the individual responsible.

Communication:

All antimicrobial stewardship committee (ASC) members are responsible for obtaining regular input from their colleagues, whom they represent, and relaying this information to ASC to ensure thorough representation of all stakeholders.

Members are required to keep their colleagues updated regarding ASC policies and protocols to ensure stakeholders remain informed.

ANTIMICROBIAL STEWARDSHIP PROGRAMME MEASUREMENT

Successful antimicrobial stewardship program include all the elements of successful quality improvement programmes and measuring the effectiveness of programme activities is a key component. Monitoring and analysis of antimicrobial usage is critical to measure the effects of stewardship interventions. Process and outcome measures should be incorporated into the AMS plan.

A. Process measures

Rate of clinician acceptance of AMS recommendations.

Rate of adherence to documentation policy at time of antimicrobial initiation (dose, duration and indication explicitly written)

Rate of review of Carbapenem and Polymyx in prescriptions by primary team at 72 hours

Rate of appropriate empirical prescription according to antimicrobial guideline

B. Outcome indicators

Specific antibiotic DDDs over every 6 months

Cost differences

For intervention results in the antimicrobial being stopped or switched to a cheaper alternative or to oral dosage form.

Formula of cost saving and days calculation -

C. Other Suggested Indicators (Where applicable)

Readmission within 30 days.

Percentage of patient with AMS recommendation accepted being re-admitted within 30 days.

Mortality within 30 days

Rates of mortality within 30 days inpatient with AMS intervention.

SWAZILAND NAZERINE HEALTH INSTITUTION - RESTRICTED ANTIBIOTICS DECLARATION FORM

<p>Patient Details</p> <p>Name: Ward:</p> <p>File number: Age: Weight: Gender:</p> <p>Serum Creatinine: mg/dl</p>
--

<p>TURN OVER FOR LIST OF RESTRICTED ANTIBIOTICS AND USAGE GUIDELINES</p>

<p>Place of acquisition of the infection: Hospital{ } Community{ }</p> <p>Underlying diseases 1..... 2.....</p> <p>Site of infection: sepsis{ } gastrointestinal tract{ } bacteraemia{ } urinary tract{ } lung{ }</p> <p>: Others, specify.....</p> <p>Predicted / known causative organism 1.....</p> <p>2.....</p> <p>Microbiology tests: Gram stain { }</p>
--

: Culture Not done

Done - Results pending

Results known as.....

Empiric use: infecting organism (s) unknown, 3 day review of therapy required

OR

Directed therapy: infecting organism(s) known, 7 day review of therapy required

INDICATION

Please tick appropriate box on reverse side. Give details below if indication not listed:

.....

Note: The antimicrobial stewardship committee or clinical microbiology may be required for other indications

CULTURE AND SENSITIVITY DATA

Organism(s).....

Sensitive to.....

Resistant to.....

REQUESTING DOCTOR:.....

PHARMACIST :..... DATE:.....

Note: Doses may require modification based on renal function

Antibiotic	Usage Guidelines
Ceftriaxone 1g	<p>Treatment of: LRTI(), URTI(), cholecystitis(), ascending cholangitis() or pelvic inflammatory disease(), under the following circumstances:</p> <p>{ } in patients hypersensitive to penicillin (excluding immediate hypersensitivity or</p> <p>{ } due to susceptible organisms (resistant to earlier generations of cephalosporin) or</p> <p>{ } where the use of aminoglycosides are contraindicated due to a calculated creatinine clearance of less than 20ml/min</p> <p>{ } Empirical treatment, with penicillin, of bacterial meningitis pending culture and sensitivity results</p> <p>{ } Acute epiglottitis, orbital/ periorbital cellulitis, and gonococcal infections</p> <p>{ } Prophylaxis for meningococcal contacts</p> <p>{ } Spontaneous bacterial peritonitis pending culture and sensitivity results</p>
Ciprofloxacin	<p>{ } Infections due to <i>Pseudomonas aeruginosa</i> or other gram-negative bacteria resistant to all other agents</p> <p>{ } Bacterial gastroenteritis in severely immunocompromised patients</p> <p>{ } Bone and Infections, epididymo-orchitis, prostatitis or perichondritis of the pinna, involving proven/ suspected gram-negative or gram-positive bacteria resistant to all other appropriate agents</p>

Piperacillin 4g	{ } Treatment of <i>Pseudomonas aeruginosa</i> infections in combination with another anti-pseudomonal agent
Meropenem	{ } Pathogen resistant to other antimicrobial agents except Meropenem { } Documented ESBL producing organism
Vancomycin	{ } For infection with methicillin-resistant <i>S. aureus</i>
Clindamycin	{ } Susceptible gram-positive infections allergic to penicillin; sensitive staphylococcal and anaerobe infections { } Severe soft tissue infections, lung abscesses, quinsy (not responding to penicillins)
Tazobactam	{ }

Policy

Clinical Guideline

Principles for rational Antimicrobial Prescribing Clinical Guideline for children

Policy developed by: Pharmacy department, Laboratory and infection Control department

Approved by: Drugs and therapeutic committee

Next review due: December 2016

Table of Contents

Summary:

The Antimicrobial Prescribing Clinical Guideline provides general principles that all RFMH Health prescribers should be aware of when prescribing antimicrobials for patients with, or at risk of, infection.

It outlines processes for to ensure optimisation of prescribing of antimicrobials in all clinical settings, ensuring antimicrobials are prescribed and utilised according to principles of evidence-based medicine.

Keywords:

Antimicrobial, prescribing, guideline, AMS, antibiotic, MINDME, optimisation, evidence, Therapeutic Guidelines, Antibiotic, Antimicrobial Prescribing Clinical Guideline

Policy history

Is this a new policy? **Y**

Does this policy amend or update an existing policy? **N**

Does this policy replace an existing policy? **N**

Staff impact

All Clinical, Medical, Nursing, Allied Health, Emergency, Dental, Pathology

Disclaimer

This document is provided as an information resource for all health care workers to assist in the appropriate prescribing of antibiotics. It attempts to summarise relevant information for clinicians from Swaziland and International guidelines as well as reference to textbooks, key publications and expert opinion.

Recommendations change rapidly and opinion can be controversial. The authors do not warrant that the information contained in this booklet is complete.

Agents available at RFMH Medicine Formulary

Antimicrobial	Oral	Parenteral	Cost
Benzyl penicillin		5.0MU	Injection: E45.60/10'S
Amikacin injection		1g/4ml, 500mg/4ml	Injection: E136.95/10's-1g Injection: E113.11/10's- 500mg
Benzathine penicillin		2.4MU	Injection: E70/10's
Procaine penicillin		300 000U /IU	Injection: E54.20/10's
Phenoxyethyl penicillin	125mg/5ml, 250mg		Tablets: 223.00/1000's Suspension: E8.99/100ml
Amoxicillin	250mg, 500mg,1g, 125mg/ml 250mg/ml	500mg	Tablets 250mg: E85.00/500's Tablets 500mg: E164.00/500's Suspension 125mg: E5.95/100ml Suspension 250mg: 8.50/100ml Injectable: E104.50/10's
Amoxicillin- clavulanic acid	125-31mg/5ml, 500-125mg	1.2g	Tablets: E26.50/15'S Suspension: E13.09 Injectable: E14.00/1's
Cloxacillin	125mg/5ml, 250mg, 500mg	500mg/5ml	Capsules 250mg: E274.10 Capsules 500mg: E260.00 Suspension: E11.78/100ml Injectable: E43.40/10's
Flucloxacillin	125mg/5ml		Suspension: E10.58/100ml
Streptomycin		1g	Injection: E150.70
Erythromycin	125mg/5ml, 250mg 500mg		Tablets 250mg: E328.90/1000's Tablets 500mg: E612.00/1000's Suspension: E7.80/100ml
Metronidazole	200mg/5ml, 200mg 400mg	500mg/100 ml	Tablets 200mg: E75.64 Tablets 400mg: E134.30/1000'S Suspension: E12.72/100ml Injectable: E10.95/100ml
Cotrimoxazole	200-40mg/5ml, 400- 80mg, 800-160mg	80/400mg /5ml	Tablets 480mg: E82.00 Tablets 960mg: E259.00 Suspension: E4.99/100ml Injectable: E349.90/10's
Cefazolin		1g	Injection: E108.90/10's
Ceftriaxone		250mg, 1g	Injection 250mg: E45.00/10's Injection 1g: E70.00/10's
Cefuroxime		1.5g,	Injection: E240/10's
Clindamycin	150mg	600mg	Injection:E199.00/100's

Ciprofloxacin	250mg, 500mg	2mg/ml	Tablets 250mg: E5.50 Tablets 500mg: E42.00 Injection: E27.20/50ml
Cefpodoxime	40mg/5ml		Suspension: E
Azithromycin	500mg		Tablets: E5.95/3's
Cefaclor	375mg, 185mg/5ml		Tablets: E69.99/15's Suspension: E49.50/50ml
Doxycycline	100mg		Tablets E193.92/1000's
Nitrofurantoin	100mg		Tablets E340.00/1000's
Dapsone	100mg		Tablets: E
Clarithromycin	125mg/5ml, 250mg, 500mg		Tablets 250mg: E207.72/100's Tablets 500mg: 51.50/14's Suspension: E69.99/50ml
Chloramphenicol		1g	Injection: E83.90/10's
Gentamycin		80mg/ml	Injection: E270.00/100's
Spectinomycin		2g	Injection: E78.00/1's

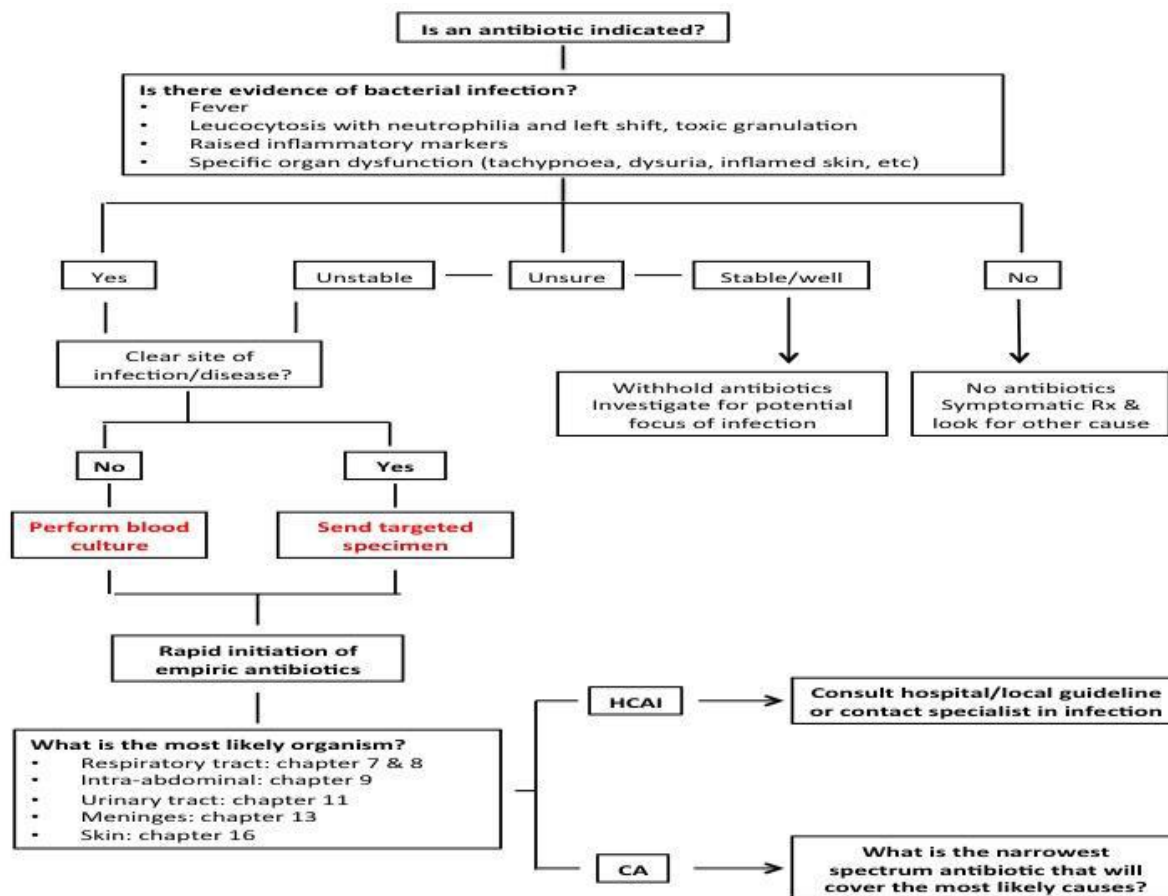
GENERAL PRINCIPLES OF PRESCRIBING ANTIMICROBIALS

Diagnosis

Consider the possible infecting pathogens and the severity of the condition to be treated. Specimens for microbiological examination should be taken before starting antimicrobial therapy. This is always important but especially in children with suspected infective endocarditis or urinary tract infections. Isolation of bacteria from a specimen does not automatically mean antibiotic treatment is required - treat the patient, not the culture result.

Principles for rational antibiotic prescribing

Decide if an antibiotic is indicated: does the patient have a bacterial infection?



Targeted refers to specimen from site of infection e.g. urine for cystitis

2. Perform cultures before administering antibiotics in hospitalised patients

This allows de-escalation to a narrow spectrum antibiotic once the antibiogram is available & is a cornerstone of antibiotic stewardship or in outpatients with recurrent infections.

3. Choose an appropriate empiric antibiotic:

a. Target the most likely pathogen(s) for the site of infection

This can be predicted by understanding the broad groups of pathogens that most commonly cause infections at various sites:

- Skin and soft tissue: Gram-positive cocci
- Urinary tract: Gram-negative bacilli
- Intra-abdominal: Gram-negative, gram-positive and anaerobic organisms
- See chapters on specific infections for more details

An appropriate empiric antibiotic can then be selected by matching the narrowest spectrum antibiotic with the likely pathogens. Spectrums of activity of commonly used antibiotics are shown below:

	Gram-positive cocci					
	Clusters			Pairs/chains		
MSSA	MRSA	<i>S. pneumoniae</i> Most other Streptococci	<i>E. faecalis</i>	<i>E. faecium</i>	VRE	
Amoxicillin/ampicillin	-	-	+	+	-	-
Cloxacillin	+	-	+/-	-	-	-
Clindamycin	+	+/-	+	-	-	-

Gram-positive cocci						
Clusters				Pairs/chains		
Ceftriaxone	+	-	+	-	-	-
Co-amoxiclav	+	-	+	/	-	-
Vancomycin	/	+	/	/	+	-
Moxifloxacin	/	+/-	+	/	+/-	-
Linezolid	/	/	/	/	/	+
Daptomycin	/	/	/	/	/	/

Gram-negative							
Bacilli				Cocci			
<i>E. coli</i> Klebsiella spp.	Enterobacter spp.	ESBL	CRE	Salmonella spp.	Pseudomonas spp.	<i>Neisseria meningitidis</i>	
Amoxicillin/ampicillin	-	-	-	-	/	-	+/-
Penicillin	-	-	-	-	/	-	+/-
Cotrimoxazole*	+/-	+/-	+/-	-	+/-	-	-
Ceftriaxone	+	-	-	-	+	-	+

	Gram-positive cocci						
	Clusters				Pairs/chains		
Co-amoxiclav	+	-	-	-	/	-	/
Ciprofloxacin	+	+	+/-	+/-	+	+	/
Aminoglycosides	+	+	+/-	+/-	-	+	-
Cefepime	/	+	-	-	/	+	/
Imipenem	/	/	/	+/-	/	+	/
Meropenem	/	/	/	+/-	/	+	/

b. Assess likelihood of antibiotic resistance

Risk factors include known colonisation with a resistant pathogen, HCAI, recent antibiotic exposure. Local resistance patterns inform prescribing.

c. Review potential contraindications

Allergy:

Clinicians should differentiate an immediate Type 1 IgE mediated hypersensitivity reaction from other less dangerous types of hypersensitivity. Classical signs of Type 1 hypersensitivity are anaphylaxis, angioedema, urticarial rash, and bronchospasm. If a type I hypersensitivity reaction to penicillin has occurred, then all β -lactam antibiotics should be avoided, unless there is no alternative drug available when penicillin desensitisation can be attempted as an inpatient.

Patients with other types of hypersensitivity reactions, usually a maculopapular rash to amoxicillin, should avoid all penicillins but may tolerate other β -lactam antibiotics like Cephalosporins. The 1st generation Cephalosporins should be avoided as they have a higher risk of cross-reactivity with penicillin, but this risk is much lower for second- or third-generation Cephalosporins (reported to be only 0.1%).

If the previous reaction to penicillin was a maculopapular rash, it is relatively safe to use 2nd/3rd generation Cephalosporins and use would depend on the patient's social circumstances and access to follow-up. In patients with a remote history of a rash on penicillin it is often difficult to differentiate a maculopapular rash from an urticarial rash; all β -lactam antibiotics should be avoided if urticaria occurred on penicillins as this is a Type 1 reaction. In this setting, skin testing before using a cephalosporin is recommended, as a positive reaction to penicillin indicates Type 1 hypersensitivity.

Toxicity:

Antibiotics can cause direct dose-dependent toxicity and should be avoided in patients at high-risk of developing organ damage with a specific agent. For example, do not use aminoglycosides in patients with renal impairment or hearing loss.

d. Choose drug with adequate target tissue penetration

Drug	CSF	Lung	Soft Tissue	Urinary Tract
Ampicillin	Good *in higher doses	Good	Good	Good

Cloxacillin	Inadequate data	Fair	Good	No data
Clindamycin	Poor	No data	Fair	No data
Amoxic-clav	Poor	Good	Good	Fair
Ceftriaxone	Good * in higher doses	Good	Good	Good
Aminoglycosides	Poor	Poor	Fair	Good
Ciprofloxacin	Good *in higher doses	Good	Good	Good
Cotrimoxazole	Good	Good	Good	Good
Imipenem	Good	Good	Good	Good
vancomycin	Poor	Fair	Poor	Good

Linezolid	Good	Good	Good	Good
Meropenem	Good *in higher doses	Good	Good	Good

e. Aim for a single drug with the desired spectrum of activity

Monotherapy is preferred unless combination therapy is required for synergy (e.g. endocarditis) or extended spectrum beyond what can be obtained with a single drug (e.g. atypical pathogens in severe CAP).

f. Ensure correct dose and route of administration

Maximal doses do not always need to be given - the dose depends on the site and severity of infection as well as pharmacokinetics of the antibiotic. Dosing recommendations have been provided throughout the booklet. Infections that commonly require higher doses include infective endocarditis and meningitis, whilst uncomplicated urinary tract infections can be treated with lower doses since the drugs used are concentrated in the urine. The oral/enteral route is preferred whenever possible for patients with mild to moderate infections. Intravenous antibiotics should be reserved for severe infection or for certain sites such as the CSF, bacteraemia, endocarditis, bone and joint infections. Monitor the child's response and consider changing from IV-to-oral therapy when possible.

g. Duration of therapy

Duration of therapy should be determined by clinical factors such as site of infection, severity of illness and response to treatment. As a general guide, antibiotics can be discontinued within 48-72 hours of the temperature returning to normal. Infections at certain sites (e.g. osteitis or endocarditis), with particular organisms or in immunocompromised individuals may require prolonged therapy. Guidelines are given in the text where this is relevant. With all antibiotics, an ongoing re-evaluation of the patient's infection should occur with the aim of stopping the antibiotic as soon as it is no longer necessary.

h. Cost

Choices often exist between antibiotics of equal efficacy and safety but differing cost. Where such a choice exists, the least expensive agent should be used whenever possible. This has been a guiding principle in the development of this document. If a more expensive agent is used empirically, a change to a cheaper, appropriate agent should be made as soon as the sensitivity report is available.

i. Antibiotic levels

Measurement of serum antibiotic levels should be routinely performed when administering aminoglycosides. Trough levels are taken just before the next dose. Peak levels are taken one hour after a bolus IM or IV, or one hour after an IV infusion is commenced. A peak level should be established as soon as possible, after the first or second dose. Once an adequate peak level has been achieved only trough levels need be monitored (usually twice a week) provided the patient remains stable. Requests for levels should be submitted to the pharmacology laboratory indicating exact times of doses and samples.

Routine measurement of vancomycin levels is indicated when treating serious infections, infections due to strains with raised MICs or when drug toxicity is a concern ("Vancomycin"21 below). Vancomycin levels should also be determined in patients with renal impairment to establish when the next dose is to be administered. The

level should be measured one to five days after the previous dose. The interval will depend on the degree of renal dysfunction. In patients with sensitive organisms, trough vancomycin levels should be maintained between 5 and 10 mg/l, but higher concentrations are recommended for organisms with higher MICs (consult with microbiology or IDs and see “Vancomycin” below). Levels should also be monitored if patients are on a combination of a glycopeptide and an aminoglycoside. This combination should however be avoided if at all possible.

5. Start the appropriate antibiotic rapidly in severe infections

Mortality increases by 8% for every hour antibiotic administration is delayed in septic shock

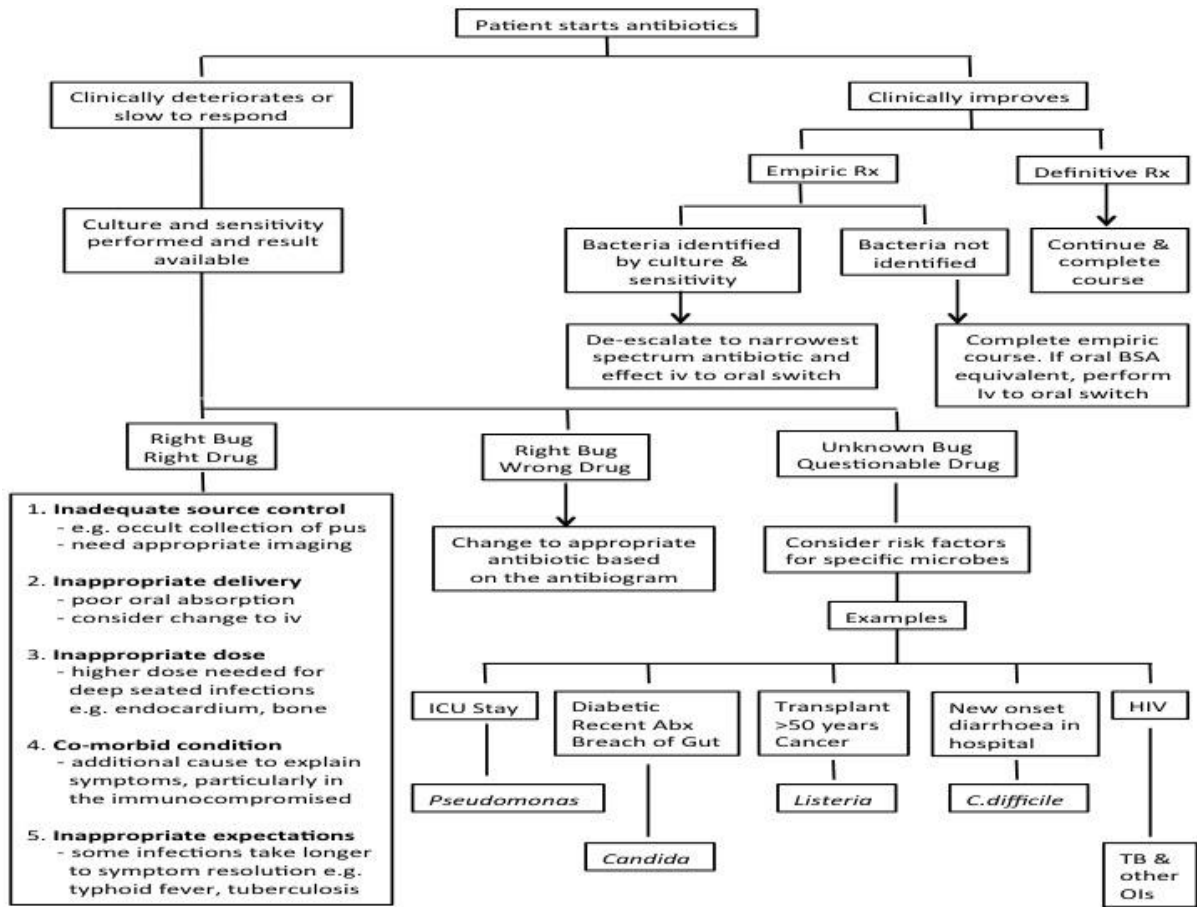
6. Practice early and effective source control

Search for and remove any persistent foci of infection

7. Evaluate antibiotic appropriateness every day

Changing antibiotics

Once antibiotics have been initiated the decision to change or stop therapy depends on the patient's clinical response and culture results (algorithm).



INDICATIONS FOR BLOOD CULTURES

1. Child with fever (axillary T > 38.5°C) with no localising signs < 3 years of age.

2. Fever with suspected: - meningitis - *complicated* pneumonia/effusion/lung abscess - pyelonephritis - arthritis/osteomyelitis/cellulitis - endocarditis/pericarditis.

3. Immunocompromised child (with fever/hypothermia) - severe protein-energy malnutrition (kwashiorkor/marasmus) - immunologic deficiency (humoral/cellular) - neoplasia - HIV with suspected severe bacterial infection.

4. Any neonate with fever ($T > 38.4^{\circ}\text{C}$)/hypothermia.

5. Infant <1 month old with diarrhoea

6. **No** blood culture for uncomplicated tonsillitis/otitis media/pharyngitis or uncomplicated acute respiratory infection including bronchiolitis / uncomplicated pneumonia

7. **No** blood culture indicated in febrile seizures where a clear focus is identified

Please Remember: ♣ always maintain strict aseptic technique and use a sterile pack when taking a blood culture

♣ Cultures must be sent in the Paediatric Bactec bottles

♣ Take 1 -2 ml of blood in a neonate and 2-5ml in an older child

♣ Remember to get appropriate specimens for culture from other sources

sputum from a child old enough to cough, especially if has chronic lung disease, bronchiectasis

urine and CSF in suspected neonatal sepsis

urine dipstix screen in all children with gastroenteritis, severe PEM, unexplained source of fever. *Sterile* specimen subsequently taken and sent for culture if dipstix suggestive of UTI.

RESTRICTED ANTIMICROBIALS AT RFMH

The use of the antimicrobials listed below is restricted and requires clearance by either a microbiologist or IDs clinician. If the prescribing clinician is of the opinion that any of these agents are required for the management of a patient in their care, they should contact the microbiologist or IDs clinician on-call for details on how to obtain clearance. Motivation should be supported by relevant clinical details and preferably microbiological evidence. The Pharmacy is authorised to deny the release or continuation of restricted agents for which the necessary clearance has not been obtained. Vancomycin levels should also be determined in patients with renal impairment to establish when the next dose is to be administered. The level should be measured one to five days after the previous dose. The interval will depend on the degree of renal dysfunction. In patients with sensitive organisms, trough vancomycin levels should be maintained between 5 and 10 mg/l, but higher concentrations are recommended for organisms with higher MICs (consult with microbiology or IDs and see “Vancomycin” below). Levels should also be monitored if patients are on a combination of a glycopeptide and an aminoglycoside. This combination should however be avoided if at all possible.

NOTES ON COMMONLY USED AGENTS

Antibacterial Agents

Aminoglycosides

The aminoglycosides in use at RCCH/TCH are gentamicin, tobramycin and amikacin. Streptomycin is reserved for treating TB and tobramycin is currently used primarily for treating *Acinetobacter* infections. Aminoglycosides have activity primarily against aerobic gram-negative bacilli. They have no anaerobic cover. They are used most commonly where infection with a gram-negative bacillus is suspected or confirmed e.g. UTI, abdominal sepsis,

severe pneumonia. Aminoglycosides have some activity against staphylococci, but are not first-line agents for treating staphylococcal infections and should not be used alone for this purpose. They can also be used in combination with either penicillin (or rarely vancomycin) to treat streptococcal or enterococcal endocarditis. If used in combination, they are used at lower than normal doses, as their action is synergistic with the other agent. Aminoglycosides should not be used for longer than 14 days, unless unavoidable. Aminoglycosides demonstrate concentration-dependent killing - the higher the serum concentration, the better the killing activity. Peak levels are thus checked to ensure a high enough concentration. They also have a post-antibiotic effect - even at low concentrations in serum, they inhibit regrowth of bacteria. Aminoglycosides can thus be given as a single daily dose, with no loss of efficacy, and reduced potential for toxicity. As discussed earlier, trough levels should be measured just before the dose is given and peak levels measured one hour after a bolus IM or IV dose, or one hour after commencing an IV infusion.

AMINOGLYCOSIDE DOSING SCHEDULE

AMINOGLYCOSIDE DOSING SCHEDULE				
THE MOST IMPORTANT DOSE IS THE FIRST ONE - DO NOT UNDERDOSE				
Antibiotic	Dose	Interval	Peak level	Trough level
Gram-negative infection - normal renal function				
Gentamycin	5-7.5mg/kg/dose	daily	>8	<1
Amikacin	15mg/kg/dose	daily	>30	<1

Gram-negative infection - poor renal function				
Gentamycin	3-4mg/kg/dose	A peak of above 8mg/l must be achieved. Repeat dose when level <1mg/l but if interval required to achieve this is >48 hours consider alternative therapy		
Amikacin	10mg/kg/dose	A peak of above 30mg/l must be achieved. Repeat dose when level <1mg/l but if interval required to achieve this is >48 hours consider alternative therapy		
Streptococcal or enterococcal endocarditis				
Gentamycin	1.5mg/kg/dose	12 hourly	3-8	<1

Carbapenems

The commonly used carbapenems are meropenem and imipenem. These are all very broad-spectrum agents, with activity against most gram-negative bacilli, Streptococci (poor enterococcal cover), cloxacillin susceptible *S. aureus* and anaerobes. These agents are reserved for infections with organisms resistant to other antibiotics and should be used very sparingly.

Cephalosporins

The available Cephalosporins at RFMH are Ceftriaxone, cefotaxime, Cefuroxime and cefepime. Cephalosporins are broad-spectrum agents, with activity against gram-positive and gram-negative organisms (but little effective anaerobic cover).

The use of Cephalosporins is strongly linked to the development of antibiotic resistance and should be used for specific indications only. They can be used where aminoglycosides may be inappropriate (e.g. due to intrinsic renal dysfunction) or for treating CNS infections. It is important to remember that Cephalosporins have NO activity against cloxacillin-resistant staphylococci as well as enterococci.

- Ceftriaxone, which may be used as a once daily intravenous or intramuscular injection, is currently the most cost-effective third-generation cephalosporin available. Roche recently released the following safety advice: “Rocephin and calcium-containing solutions, including continuous calcium-containing infusions such as parenteral nutrition, should not be mixed or co-administered to any patient irrespective of age, even via different infusion lines at different sites. As a further theoretical consideration and based on 5 half-lives of ceftriaxone, Rocephin and IV calcium-containing solutions should not be administered within 48 hours of each other in any patient”. This recommendation was made following reports of intravascular or pulmonary precipitations in neonates, treated with Ceftriaxone and calcium-containing IV solutions.
- Cefotaxime is an alternative to Ceftriaxone.
- Cefuroxime is used orally to treat UTIs.
- Cefepime’s primary indication in children is for treating suspected or confirmed infections with *P. aeruginosa*.

Cotrimoxazole (trimethoprim + sulfamethoxazole)

Traditionally regarded as an antibacterial agent and widely used as such, although widespread resistance has developed and few bacterial organisms remain susceptible. In instances where a pathogen is known to be susceptible to cotrimoxazole, it remains a useful and effective agent. Cotrimoxazole also has activity against other pathogens and its main current indication is for the prophylaxis and treatment of infections due to *Pneumocystis jiroveci* in immunocompromised patients. Also used in treating nocardiosis, prophylaxis and treatment of toxoplasmosis and *Isospora belli* diarrhoea. Well absorbed orally and widely distributed. Not

recommended in infants under 4-6 weeks of age due to increased risk of hyperbilirubinaemia and kernicterus. There is a wide spectrum of potential side effects; sulfamethoxazole is more frequently implicated in hypersensitivity reactions and gastrointestinal disturbances.

Macrolides / Lincosamides

The macrolides (erythromycin, clarithromycin and azithromycin) and lincosamides (clindamycin) are not structurally related but are often linked together as they share very similar mechanisms of action, and thus cross-resistance can exist. The spectrum of activity of the macrolides includes gram-positive organisms (staphylococci, Streptococci and some corynebacteria), atypical organisms (Legionella, Chlamydia and Mycoplasma) and *Campylobacter* spp. It must be remembered that amongst isolates of *S. pneumoniae* and *S. aureus*, resistance to these agents is well described. There is some (limited) evidence that azithromycin can be used to treat cryptosporidiosis; however, its efficacy is variable. The newer macrolides have a similar spectrum to erythromycin and do not have the same degree of GIT side effects as erythromycin; however, they are also more expensive.

Clindamycin has activity mainly against staphylococci and Streptococci, as well as many anaerobic bacteria. Pneumococcal resistance to clindamycin is less common than to erythromycin, but staphylococcal resistance to clindamycin is unfortunately becoming more common amongst nosocomial isolates. However, for community-acquired cellulitis / soft tissue infections clindamycin is still a very good agent, and some would consider it the drug of choice for necrotising fasciitis.

Neither the macrolides nor lincosamides have any effective enterococcal activity.

Metronidazole

Bactericidal and is indicated for treating anaerobic infections including peritonitis and necrotising enterocolitis (but excluding actinomycosis). It also has antiprotozoal activity

Penicillins

Penicillin / amoxicillin / ampicillin effective against all *S. pyogenes*, most other Streptococci, enterococci and many anaerobes. Reduced susceptibility is an increasing concern amongst pneumococci, but these agents are still the best options for treating infections outside the CNS (e.g. pneumonia, otitis media) caused by *S. pneumoniae* with intermediate resistance to penicillin/ampicillin. Amoxicillin/ ampicillin are also effective against most *H. influenzae* isolates.

Cloxacillin

This agent is primarily used to treat staphylococcal infections, and if the isolate is sensitive to cloxacillin, cloxacillin is the best agent. It is worth remembering that cloxacillin susceptible staphylococci are susceptible to most other beta-lactams (except penicillin / amoxicillin / ampicillin). Thus, in cases of a mixed infection, co-amoxiclav or a cephalosporin can be used to successfully treat a staphylococcal infection. However, the converse is also true - staphylococci that are resistant to cloxacillin are resistant to ALL beta-lactam agents.

Amoxicillin-Clavulanic Acid

This is a relatively broad-spectrum agent that is available in both oral and IV formulations (IV not available at RCCH). Its spectrum includes Streptococci, cloxacillin susceptible staphylococci, haemophili, gram-negative bacilli and anaerobes. Its main indications are for treating urinary tract infections, dental infections, bite wounds and as a second-line agent for otitis media (if amoxicillin alone has failed). Current paediatric oral preparations contain amoxicillin and clavulanic acid in a ratio of 4:1. When using higher dosage ranges (>15 mg/kg/dose), add amoxicillin separately to limit the clavulanic acid dose and minimise risk of gastrointestinal side effects.

Piperacillin-tazobactam

This broad-spectrum agent is only available intravenously, and the spectrum is much the same as co-amoxiclav. However, it has a broader gram-negative spectrum than co-amoxiclav, and will provide cover against some *Acinetobacter* and *Pseudomonas* species as well as many of the enteric gram-negative bacilli. It should only be used for treating suspected or confirmed nosocomial infections, or if a community-acquired infection with *Pseudomonas aeruginosa* is suspected.

Penicillin allergy

There are usually alternatives to penicillin if there is a documented history of penicillin allergy. However, it is important to take a detailed history of the allergic reaction, as many supposed allergic reactions do not represent true allergy.

Alternatives to penicillin include:

- Erythromycin
- Clindamycin (especially for skin and soft tissue infection)
- Vancomycin (primarily for treating enterococcal infection)
- Cephalosporins (pneumonia and abdominal sepsis)

There is approximately a 5-10% chance of cross-reactivity with a cephalosporin. If there is a documented history of severe penicillin allergy (e.g. anaphylaxis), all Cephalosporins should be avoided. If a cephalosporin is considered, a cephalosporin with a different side-chain from the offending penicillin should be used. Cefuroxime has a unique side-chain and can be used in cases of side-chain allergy. If in doubt about suitable alternatives, please consult the microbiologist, IDs unit or allergy service.

Quinolones

The fluoroquinolones, ciprofloxacin and ofloxacin, are all very effective agents for treating gram-negative infections. Nalidixic acid is only available orally, and is used to treat mild dysentery. Ciprofloxacin and ofloxacin also have very good activity against legionella, neisseria and haemophili, and some activity against staphylococci and chlamydia, although they are seldom used on their own for the latter two organisms. They provide no effective anaerobic cover and have unpredictable activity against gram-positive organisms. They are available orally or IV. Oral bioavailability is equivalent to IV, and they should thus be administered orally unless there are clinical reasons that the drug may not be absorbed (e.g. ileus, severe vomiting and/or diarrhoea etc.). Ciprofloxacin is used to treat various resistant gram-negative organisms, including *P. aeruginosa*. When used to treat *Pseudomonas* infections, a higher dose should be used. Ofloxacin is used primarily as part of combination therapy for MDR-TB. The use of ciprofloxacin should be limited to specific indications and primarily guided by antibiotic sensitivity results. Some of the newer fluoroquinolones (e.g. moxifloxacin) have better activity against gram-positive organisms, including Streptococci. These are not yet available at RCCH/TCH.

Vancomycin

Vancomycin is not an aminoglycoside, it is a glycopeptide, and only has activity against gram-positive organisms. If a *Staphylococcus* is sensitive to cloxacillin, cloxacillin is a more effective agent than vancomycin. Vancomycin must be given by slow intravenous infusion over at least 1 hour to avoid the “red man syndrome”, which is due to histamine release. As the dose of vancomycin appropriate for each patient is dependent on the MIC of the organism being treated, it is essential that every attempt be made to identify the suspected pathogen. Before vancomycin therapy is considered suitable specimens (including at least TWO blood cultures) must be submitted to the microbiology laboratory. Vancomycin levels remain a somewhat contentious issue - both with respect to whether they should be measured, and what constitutes the therapeutic range. Much of this debate revolves around the observations that clinical outcomes tend to be worse when treating strains with higher (although still sensitive) MICs of 1 or 2 mg/l. In these instances, some authors have recommended aiming for higher trough levels of 15 mg/l or administering as a continuous infusion. Routine measurement of vancomycin levels is not necessary when treating strains with low MICs (<1.0 mg/l), unless the patient has renal dysfunction, is on other

potentially nephrotoxic agents (e.g. aminoglycosides), is on unusually high doses of the antibiotic (e.g. obese patients) or is not responding to the treatment. Combinations of vancomycin and aminoglycosides should be avoided wherever possible. In cases of renal failure (especially in patients on dialysis), levels are measured to determine when to administer the next dose.

Gastrointestinal infections	
Amoebiasis	Metronidazole 15 mg/kg/dose 8 hourly x 10 days
Bacterial dysentery	Nalidixic acid 12.5 mg/kg/dose 6 hourly PO x 3-5 days. If ill and toxic or <3 months of age: Ceftriaxone 50 mg/kg/dose once daily IV x 5 days
Cholera	Ciprofloxacin 20 mg/kg/dose as a single dose PO Note: 1. An alternative for children >8 years of age is doxycycline 4 mg/kg/dose as a single dose PO 2. Antimicrobial susceptibilities of newly isolated organisms should be determined 3. Oral or parenteral rehydration therapy to correct dehydration and

	<p>electrolyte abnormalities is the most important modality of treatment</p> <p>and should be initiated as early as possible</p>
Cryptosporidium	No effective therapy
<p>Diarrhoeal disease</p> <p>Acute (<5 days)</p> <p>Persistent (>5 days)</p>	<p>NIL</p> <p>Cholestyramine: <6 months of age 500 mg; >6 months of age 1 g 6 hourly</p> <p>PO x 5 days + gentamicin 10 mg/kg/dose 4 hourly PO x 3 days (maximum dose 60mg)</p>
Giardiasis	<p>Metronidazole 7.5 mg/kg/dose 8 hourly PO x 5 days</p> <p>May also be used as a once daily dose according to age:</p> <p>1-3 years of age: 500 mg</p> <p>3-7 years of age: 600-800 mg</p> <p>7-10 years of age: 1 g</p> <p>An alternative over the age of 2 years is albendazole 400 mg once daily</p> <p>PO x 5 days</p>

Giardiasis Peritonitis / necrotising enterocolitis	Benzyl penicillin 50 000 U/kg/dose 6 hourly IV + gentamicin 7.5 mg/kg/ dose once daily IV + Metronidazole 7.5 mg/kg/dose 8 hourly IV
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ADMISSION & REFERRAL POLICY

Rehydration room is an emergency room for the management of acute complications of diarrhoeal disease i.e. Hypovolaemia shock, Dehydration and Electrolyte imbalances.

The room is not appropriate for admission of patients with the following problems:

Those needing intensive care

Neonates with diarrhoea

Short bowel syndrome

Persistent diarrhoea > 2 weeks who are not dehydrated and do not have nutritional issues -can be investigated and managed as outpatients

The criteria for referral to L1 (general admission), L2 (Special admission) or L3 (Sub-special admission) is as follows:

Level 1 PATIENT

Common mild electrolyte disorders

Lactose intolerance

NG and IV Rehydration

Uncomplicated dysentery

Step down care if >3 months. Stable children <3 months can be considered.

Level 2 PATIENTS (Patients Who Require Specialist Care)

Prolonged (>1 week)/recurrent diarrhoea

Diarrhoeal disease with encephalopathy

Diarrhoeal disease with seizures

Diarrhoeal disease with extreme or persistent acid-base or electrolyte deviations

Recurrence of shock

<3 months (Only if unstable)

Level 3 PATIENTS (Patients Who Require Subspecialist Care)

Persistent diarrhoea (acute diarrhoea, of presumed infectious origin, lasting longer than 2 weeks) failing standard therapy

Diarrhoea of duration longer than 4 weeks in any patient

Malabsorption syndromes

Level 2 Patients with exceptions

patients who should be seen by a doctor not less than three times a DAY (These are patients who have the highest diarrhoeal disease mortality)

HIV-infected patients - particularly those who are not HAART

Severe malnutrition

HWZ <-3

MVAC < 11mm

Oedematous malnutrition

Duration more than 2 weeks, not responding to standard treatment.

Duration > 7 days in hospital - consult Paediatric Gastroenterology.

Presence of severe comorbidity: Severe pneumonia or septicaemia.

PRINCIPLES OF MANAGEMENT OF DIARRHOEAL DISEASE

Identify and treat **shock** first (triage)

Do a thorough clinical assessment to determine

Degree of dehydration (severe/some/none)

Complications

Dehydration

Neurological sequelae

Metabolic acidosis

Electrolyte disturbances

Hyper- and hyponatraemia, hypokalaemia

Susceptibility to reinfection

Malnutrition

HUS

Iatrogenic - complications fluid administration

Death

Associated illnesses or Risk Factors

small infant < 2 months

malnutrition

immune compromised

pneumonia/sepsis/UTI etc.

Decide on method of rehydration: enteral (ORT or NG) or intravenous (IV)

Decide on type of fluid

Decide on volume and rate of fluid

Frequent reassessments of the hydration status of the child

Decide level of care required (home/admit GG/refer)

IDENTIFY AND TREAT SHOCK FIRST (TRIAGE)

Triage relates to the emergency signs

A Airway

B Breathing

C Circulation

Coma (use AVPU)

Convulsion

D Dehydration (severe)

DEFG Do not Ever Forget Glucose.....check

METHODS OF REHYDRATION

ORS TRIAL

Whilst being assessed/triaged in outpatient area the child should be given 10ml of ORS (by syringe, teaspoon or cup) every 5-10minutes and gradually increase the amount as tolerated, in the ORT corner.

Children should only be admitted if they have failed an adequate observed trial test of oral rehydration in the ORT corner and are $\geq 5\%$ dehydrated/have “some/moderate dehydration”.

Oral rehydration (“ad lib” ORS) can continue to be given throughout the subsequent admission unless they have shock, depressed level of consciousness or paralytic ileus. Breast feeding infants should continue to breastfeed.

NASOGASTRIC REHYDRATION

The method of choice of initial rehydration in **all** children with moderate dehydration (5%) and **some** children with severe dehydration (10%) i.e. those without associated shock (e.g. with malnutrition, not vomiting).

In the following situations **INTRAVENOUS REHYDRATION** is indicated:

circulatory shock

paralytic ileus(abdominal distension, no bowel sounds, severe vomiting)

severe/10% dehydration with profuse diarrhoea and vomiting fluids (an alert thirsty child with severe dehydration does not necessarily need a drip)

depressed level of consciousness, severe hypotonia

vomiting/not tolerating continuous Nasogastric ORS

child <3months with severe dehydration and/or suspected sepsis

failed Nasogastric rehydration(vomiting or not improving)

FLUID TO BE USED

IVI ½ DD unless otherwise indicated (Electrolyte disturbances)

ORS/Sorol -pre-packed 200ml containers for continuous NG

MANAGEMENT OF SHOCK DUE TO DEHYDRATION (INTRAVASCULAR DEHYDRATION)**1. Assessment of Shock**

	Shock	Some/moderate dehydration
Level of consciousness	Depressed ill/weak	Normal
Peripheral pulses	Absent or Palpable but weak	Palpable
Capillary refill time	> 3 secs	< 3 secs
Pulse rate	>120 / min	Usually < 120 / min
Clinical dehydration	Normal - > 10 %	< 10 %

2. Shock management

See shock management protocol

Remember:

If unable to get an iv line up rapidly, use **intra-osseous** infusion

Investigations (after resuscitation or during if poor response) - blood gas, Na, K, urea/creat

Keep the child nil per mouth for 4-6hours

Monitor urine output

A shocked child is critically ill and must always have a doctor or experienced member of nursing staff with them at any time

Once the shock is corrected, proceed with rehydration

If the shock is not corrected after 40-50ml/kg boluses of fluid, then the child must most likely be commenced on inotropes and discussed with the ICU

There is no role for sodium bicarbonate in resuscitation for hypovolaemic shock

There is no role for SHS as a volume expander in hypovolaemic dehydration from gastroenteritis

Intra-osseous needle insertion

Needle inserted into the bone marrow of the tibia

Effective and easy

Use for emergencies and replace when an IV line can be set up preparing

Flat surface of tibia runs on inner surface of the lower part of the leg

There is a sharp blade of bone at the front of the shin

Position leg with hips slightly open and some padding under the knee.

position: 2cm below tibial tuberosity

Prepare your equipment:

Wear gloves

Clean skin with antiseptic solution

Hold leg firmly with left hand: DO NOT hold the leg BEHIND the site of insertion

Hold base of needle in palm of right hand so you can push with the palm

Keep fingers of right hand about 1cm behind the tip

Place needle through skin at right angles to bone until it rests on the bone

Press firmly though the bone with palm of your hand, using the fingers to twist the needle so that it advances more easily

Stop when you feel a sudden give and your fingers hit the skin!

Make sure your own fingers are out the way!

Remove stylet and aspirate marrow (can do dextrostix and blood culture if available)

Needle remains upright without support

Inject 10 ml of normal saline with ease

Commence infusion: fluid flows quite easily without signs of subcutaneous infiltration

Clamp a cord clamp at the base of the needle against the skin

Strap the cord clamp (and attached needle) with strapping either in a spiral or around leg but leave a small gap at the back

Strap the fluid tubing to the leg separately so that if someone pulls on the line it does not pull on the needle

If you have a proper self-threading bone marrow needle this can be used and nor strapping is necessary

Same principle and twisting and feeling a “give”

REHYDRATION IN EXTRAVASCULAR DEHYDRATION

A. **Method** - IV or Nasogastric - see before (II)

B. See Management of sever dehydration protocol

C. **Fluid volume and rate.**

(a) INITIAL FLUID VOLUME AND RATE (Flow Chart Appendix 3)

Rapid Nasogastric rehydration over 4 hours is given to all children with moderate or severe dehydration EXCEPT those with:

1. Age under 3 months.
2. Lung or cardiac disease e.g. pneumonia.
3. Suspected or proven hypernatraemia ($\text{Na} > 150 \text{mmol/l}$).
4. Overt malnutrition (NG slow over 24hrs).
5. Meeting the criteria for intravenous (page before).

NB Very important:

These children 1-4 must not then have IV but have **slower** rehydration *enterally*

The children needing Intravenous can also be rehydrated rapidly over 6-12 hours unless they meet the criteria 1-4 above -then slow iv over 24hrs

a) Calculate the **rehydration** volumes for the **first FOUR (4) hours:**

“5%” dehydrated (i.e. IMCI “some dehydration”) **-15-20 ml/kg/hour** (give the higher volume to children with a history of profuse diarrhoea)

“10%” dehydrated (i.e. IMCI “severe dehydration”) **20-30 ml/kg/hour**

NG - Set in-line manual controller to this rate **in mls per hour**

IVI - Set infusion pump to this rate **in mls per hour**

b) Continue breast feeding and small volumes of ORS. Formula milks should not be given during the first 4 hours of rehydration but should be started after that.

Note: These fluid rates incorporate maintenance, rehydration and ongoing losses for the first 4 hours (breast feeding to continue)

(b) ONGOING FLUID MANAGEMENT

a) **Review 1-2 hourly** (e.g. is the child vomiting?). Full re-assessment at **4 hours**:

- **Dehydrated to the same degree:** As above, with higher infusion rate

- **Hydration worse:** on NG, change to IV; on IV, increase the rate

- **Hydration better:** reintroduce **full feeds** ((b) on p6 for volumes), give liberal ORS (≥ 50 ml per loose stool), **and reduce infusion to 10 ml/kg /hr**

b) Review every **6 hours** thereafter till discharge:

The infusion should be stopped if

Weight is maintained, and the child is drinking

If the child then maintains weight can be discharged

(c) SLOWER Rehydration in Extravascular Dehydration in certain patients

Which patients require slower rehydration over 24 hours?

1. Age under 3 months (if sepsis likely)
2. Lung or cardiac disease e.g. pneumonia
3. Suspected or proven hypernatraemia (VII Electrolyte disturbances)
4. Overt malnutrition (never IV unless shocked)

FLUID TO BE USED

Nasogastric ORS in pre-packed 200ml containers

IVI Give 1/2 DD unless otherwise indicated (VII Electrolyte disturbances)

FLUID VOLUME AND RATE

a) Calculate the **maintenance** volume

Less than 1year 120 ml/kg/day

1-2 years 100 ml/kg/day

2-4 years 85 ml/kg/day

4 years and older 70 ml/kg/day

b) Calculate the **rehydration** volume.

“5%” dehydrated (IMCI “some dehydration”) 50 ml/kg

“10%” dehydrated (IMCI “severe dehydration”) 100 ml/kg

c) Estimate **ongoing losses** (if history of large output diarrhoea)

A child with severe diarrhoea loses at least 50ml/kg/24hrs or 10-20ml/kg/loose stool

d) **Add volumes b) and c) together as well as any part of the maintenance from a) that you have decided to give iv or NG together** and divide by 24hrs to get mls per hour given iv/ continuous NG.

(If choosing oral route can also divide volumes into 12 or 8 to be given 2 or 3 hourly but it must be ensured that this is communicated to the nurses and actually given. The continuous Nasogastric route with a volume per hour given through the rate controller is ideal for optimal absorption

Write the fluid and rate required in the fluid schedule in the notes and on the Fluid Chart.

NB: This is only an ESTIMATE of fluid requirements and is a starting point.

Repeated review and adjustment of fluid rates according to clinical assessment is essential.

Many children require more fluid for ongoing losses.

Children must be weighed and have their hydration status checked six hourly

D. In the acute setting there is no role for **sodium bicarbonate** to be used in dehydrated children with persistent acidosis, this is usually an indication that they are getting insufficient fluids, and fluid volumes must be increased. There are however times when it is given for correction of a persistent acidosis in children with suspected renal tubular dysfunction or bicarbonate depletion from excessive stool losses. The use of bicarbonate must be discussed with the consultant or senior registrar. If a transient renal tubular acidosis is suspected it can be replaced orally, otherwise half corrected over $\frac{1}{2}$ -1 hour intravenously.

V. GUIDELINES FOR INVESTIGATIONS

1. Biochemical

Biochemical tests should only be conducted in the following circumstances and only after rehydration has been commenced

1. Shock - acid-base, Na, K, urea/creatinine (AFTER resuscitation)
2. 10%/severe dehydration - Na, K, urea/creatinine +/- gas
3. Altered level of consciousness - Acid-base, Na, K, glucose, urea/creat
4. Convulsion - glucose, Na, K, Creatinine, (Ca, Mg, Pi if recurrent)
5. Unexplained hypotonia/poor head control -Na, K, Urea,Creat
6. Ileus/abdo distension - Na, K, Urea, Creat
7. Protracted vomiting with little or no diarrhoea - acid-base, Na, K, Cl, Creat
8. Anuria despite rehydration - Na, K, Urea/creat
9. Kwashiorkor - see kwashi protocol for blood tests
10. Chronic diarrhoea - Na, K, Urea/creat, Ca MgPi
11. Dysentery - see protocol

12. Other: suspected hypernatraemia(e.g. incorrect SSS mix, clinical picture worse than apparent dehydration, rubbery skin, very irritable) Na, K, Urea, creat

2. Stool Microscopy and Culture

Most diarrhoea is caused by rotavirus or and E.coli which cannot be routinely cultured from the stool. Therefore **MC&S should ONLY be conducted in the following circumstances:**

1. Dysentery
2. Persistent diarrhoea (>2 weeks), especially if HIV positive
3. Study of epidemic/outbreak (microbiology input)
4. Severe malnutrition

Note: Antibiotics are only routinely used in dysenteric forms of diarrhoea

3. Urine Tests

Dipstix testing of bag specimens commonly gives false positive results for possible infection. A negative result is very helpful in excluding infection. Dipstix is therefore not routine but should be conducted when there is a reasonable likelihood of a UTI:

1. Suspected Sepsis with unexplained fever >38 degrees(protocol)
2. Prolonged diarrhoea(>1 week)

3. Failure to thrive

If dipsticks on a bag specimen is suspicious of a UTI(nitrites/leukocytes), the test must be repeated on a catheter specimen or Suprapubic specimen. (*UTI protocol*). Only if this specimen suggests infection should the sample be sent for microscopy and culture. **Do not send bag specimens for MC&S.** Note that most Suprapubic punctures will usually be dry in dehydrated children.

Each test adds to the cost of the admission - it is a waste of resources (Dr time, parent's and states money, child's discomfort) to do a test that will not add to the child's welfare. Remember the value of frequent clinical re-assessment

4. When to perform septic work-up in dehydrated child with gastro

1. Child sicker than can be accounted for by dehydration alone: -urine dipstix (culture if abnormal dipstix), FBC, Blood culture (below), consider CSF(may need to be delayed)

2. Infant under 3 months of age: urine dipstix, bld culture, FBC, CSF, CXR

b. **Note:** CSF must be conducted in any child with gastro <1month and most <3months (but never perform LP in shocked/unstable child - delay and cover with antibiotics)

3. Unexplained fever>38.5 degree celsius - dipstix, FBC, blood culture

4. Persistent or recurrent circulatory shock: -dipstix, blood culture, FBC

5. Kwashiorkor/severe protein-energy malnutrition (*Kwashiorkor protocol*)

6. Unwell child with dysentery

Note:

i) Children with HIV infection do not require investigations for infections unless they fulfil the above criteria

ii) **CRP is not helpful in decision making** in these circumstances so must not be done please (give antibiotics if meet the indications below)

Antibiotics are not routine but are indicated in:

1. Suspected sepsis(meet criteria 1-5 above)

a) ampi/genta if meningitis excluded/not suspected

b) Ceftriaxone(100mg/kg/dose daily) if meningitis cannot be excluded and the child is too unwell to perform a lumbar puncture or has renal impairment

2. Blood in stool

3. Pneumonia (ampi/amoxil, add genta if <6months)

4. Kwashiorkor

5. UTI

6. Otitis media

7. In certain children with HIV infection(protocols/discuss with Reg/consultant)

8. In **chronic diarrhoea**(> 5days) children should be put on the *bowel cocktail*

Cholestyramine 1g po 6hrly for 5 days +

gentamicin 50mg/kg/DAY 4hrly(max 60mg/dose or 360mg/day)

Plus Metronidazole 7.5mg/kg/dose tds for 5 days

OR if strongly suspect giardiasis(child>1 year, diarrhoea for 1-2weeks):give Metronidazole <15kg -500mg po daily for 5 days, 15-22kg - 800mg po dly for 5days, >22kg - 1g po daily X 5 days, adult 2g po daily for 5 days

REMEMBER: to **stop antibiotics** if sepsis is proved unlikely or downscale from Ceftriaxone (to ampi/genta or appropriate oral antibiotic) if lumbar puncture is normal

Taking a blood culture

The younger and sicker the child, the more useful is a positive or negative blood culture result. However a blood culture is only indicated in gastroenteritis if:

1. < 3months of age and pyrexial/ill
2. <1 month old(by definition a neonate and diarrhoea could indicate parenteral sepsis)
3. Suspected bacterial meningitis
4. Kwashiorkor

5. Older “septic-looking” very unwell/pyrexial child e.g. with dysentery

Blood cultures MUST be taken with aseptic technique, with a minimum volume of 1ml in a neonate and 3-5ml in older child to increase the yield.

Always consider if the blood culture result might alter management and remember the dangers of false positives in terms of cost in lab, unnecessary exposure to antibiotics and prolonging hospital stay.

VI. ROUTINE MEDICATION

1. Vitamin A.

These dosages are given as on the road to health card. They should be given if there is no evidence/signature for a dose having been given in the last 3-6 months. Record the dose given on the RTHC

2. Potassium chloride orally

Potassium chloride 250 mg tds orally for 2 days(125mg/dose < 3 months of age). Omit in children who have been recently shocked or if there are renal concerns

3. Zinc (elemental)

Zinc supplementation shortens the duration of acute and persistent diarrhoea

Dose: 20 mg po dly (10mg dly in children under 6 months of age)

4. Immunisation

Give measles immunisation to all children>6months if no proof of immunisation.

Immunise all others on discharge if behind on schedule (check RTHC)

ELECTROLYTE DISTURBANCES

1. Hyponatraemia

If Na < 125 mmol/l

- a) If on ivi fluids: Normal Saline 200ml bag + 2ml 15% KCl+ 20ml 50% dextrose, at usual rate for rehydration (Do not correct rapidly with hypertonic(5%) saline)
- b) If NG fluids: continue with Sorol and recheck Na in 4 hours. If Na fallen further then change to ivi fluids as above
- c) Once Na > 130 mmol/l change back to ½ DD

2. Hypernatraemia

If Na > 150 mmol/l

- a) Use ½ DD (NOT 5% dextrose water) for rehydration. Treat shock with volume expanders as usual
- b) Calculate fluid administration rates as usual according to clinical dehydration, remembering that it is easy to underestimate dehydration in hypernatraemia. Rehydrate over 24hours (not 6hrs nor 48hrs)
- c) **Check serum Na 4-6 hourly if Na > 155 mmol/l.** The sodium level should drop by 1-2mmol/hr. Too rapid a fall leads to cerebral oedema and convulsions, whilst failure of the sodium level to drop means the patient needs more fluid per hour i.e. if not going down by 1-2mmol/hr increase fluid rate. Do not administer extra sodium bicarbonate. If Na > 165 mmol/l get ward bed for child
- d) Ensure hypovolaemia is corrected. Urine output should be > 2ml/kg/hr. Watch for rhabdomyolysis

3. Hypokalaemia

If $K < 3\text{mmol/l}$ OR $K < 4\text{mmol/l}$ and $BE > -10$

i) KCl 100mg/kg/dose 6hrly orally X 2 days (maximum 750mg 6 hrly or 3g daily)

If $K < 2,0\text{mmol/l}$

i) Oral KCl as above

ii) Iv KCl: 2ml KCl(15% solution) added to 200ml 1/2DD. Do not exceed this dose

iii) Check potassium level 4 hourly

If $K < 1,5\text{mmol/l}$

i) As for i) and ii) above

ii) ECG monitor

iii) Inform registrar and try to arrange high care /ICU bed for possible more rapid correction especially if child very symptomatic

4. Hyperkalaemia

If $K > 6,0\text{mmol/l}$ in face of normal base deficit

i) stop all K containing fluid including 1/2DD iv and orally, and check drug chart for any oral KCl

ii) correct any acidosis with sodium bicarbonate

iii) if > 7 mmol/l or symptomatic, ECG monitor, treat with iv calcium gluconate(0,5ml/kg), oral/rectal kayexalate, salbutamol neb

iv) ensure renal function has been checked and apply urine bag/insert catheter to monitor urine output

v) inform registrar

VIII. SPECIAL SITUATIONS

1. When the Registrar Should Be Called for Admission to ward bed or ICU:

1. Persistent shock

2. Altered LOC despite correction of shock

3. Bile-stained vomiting or marked abdominal distension

4. Convulsions

5. $K^+ < 1,5$ or > 6 mmol/l

6. $Na^+ < 120$ or > 165 mmol/l

7. pH $< 7,0$ or $> 7,40$

8. pH $< 7,15$ plus $Na > 150$ mmol/l

9. pa CO₂>6,5kpa

2. Blood in Stool/Dysentery

1. Send stool MC&S

2. Nalidixic acid(12,5mg/kg/dose 6 hrly po X 5 days) if reasonably well and able to take well orally

3. Ceftriaxone 50mg/kg/dose daily ivi X 3-5days if toxic/ill/unable to take orally

4. Follow-up in 3 days at local clinic to ensure recovery and mother/clinic Sr can phone in for stool culture results (Shigella dysenteriae can lead to HUS, or result in PLE or a more protracted course.) Parents must be told to return immediately if the child's condition changes/deteriorates

*Keep the differential diagnosis of dysentery in mind especially **intussuseption***

3. Abdominal Distension or Bile-Stained Vomiting

Ileus is usually a result of intestinal infection or hypokalaemia BUT surgical causes must be excluded including:

c. Malrotation

d. Volvulus

e. Intussuseption

i) Keep NBM, ivi fluids only, NGT on open drainage

ii) Investigations: Abdominal X-ray, electrolytes

iii) Discuss with registrar/consider surgical consult

4. Nutritional Problems

1. Kwashiorkor or marasmus - needs admission to a different cubicles

2. UWFA, FTT owing to poverty or poor nutrition practices - refer complex issues to dietician

5. Chronic diarrhoea

Chronic diarrhoea is when the child has had loose stools for > 5days.

Children should be put on the **bowel cocktail**

Cholestyramine 1g po 6hrly for 5 days +

gentamicin 50mg/kg/DAY 4hrly(max 60mg/dose or 360mg/day)

Plus Metronidazole 7.5mg/kg/dose tds for 5 days as part of bowel cocktail

OR if strongly suspect **giardiasis**(child>1 year, diarrhoea for 1-2weeks):give Metronidazole <15kg -500mg daily for 5 days, 15-22kg - 800mg daily for 5days, >22kg - 1g po daily X 5 days, adult 2g po daily for 5 days

Consider sending stool reducing substances and changing the milk to low lactose containing (pellargon) or lactose free(infasoy) if reducing substances positive or acidic pH. If changed to infasoy needs secondary level bed as will

need to be challenged in hospital unless parents can afford soya for 2 weeks at home then to change back to normal milk after 2 weeks at home

IX. ASSESSMENT FOR DISCHARGE

The child is usually ready for discharge if:

1. Discharge weight > admission weight
2. Bright eyed and alert
3. Drinking well
4. No vomiting in recent hours
5. Plans for other problems do not require inpatient care

Patients who cannot be discharged after 2 nights in GGr should be admitted elsewhere as well as those who you anticipate will not meet these criteria within 48hrs

Follow - up:

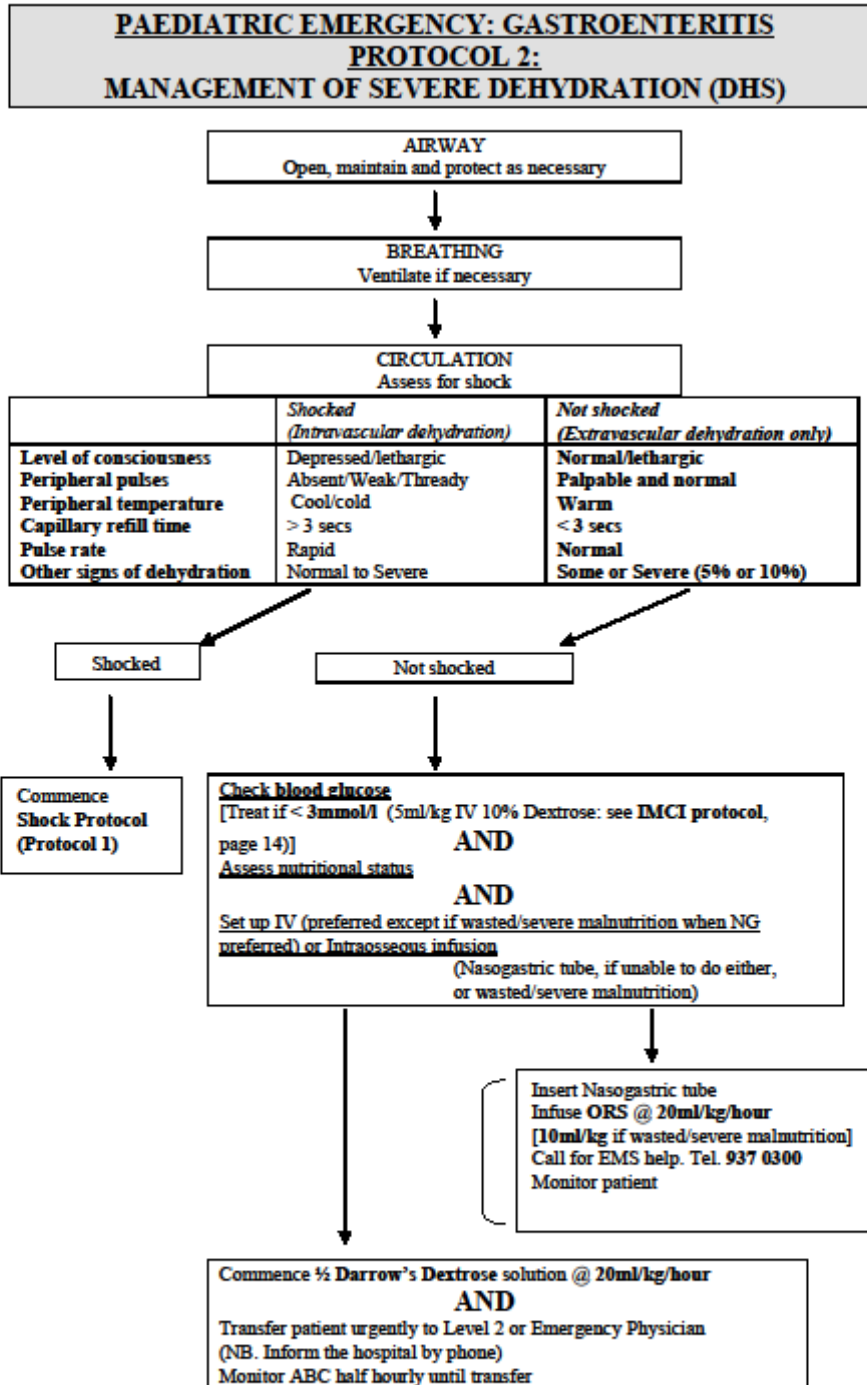
- i) Stools resolved: advice re an extra meal a day for a week. No follow-up required but encourage regular clinic attendance for weights, immunisations, vitamin A etc
- ii) Stools still loose or concerns re weight loss: refer for weight and hydration check at local clinic the following day

iii) Dysentery- as outlined above

iv) Other problems present: follow-up at Primary Care service (e.g. nutrition clinic, local authority clinic unless specific issues requiring input at TBH required)

Always plot the discharge weight on the RTHC and make an entry on the RTHC about admission

Always reinforce to the parents that should the child's condition change/ deteriorate at home, including vomiting of all fluids, not taking in any fluids, becoming drowsy/less responsive/ etc to return to the local clinic immediately for re-evaluation



This algorithm is consistent with ETAT-SA and has been endorsed by the Department of Health, Western Cape Diarrhoea Task Team and the Emergency Medicine Services.
Date of issue: November 2011
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PROTOCOL FOR THE Inpatient MANAGEMENT OF CHILDREN WITH SEVERE ACUTE MALNUTRITION AT RFMH

“Severely malnourished children are different from other children so they need different treatment”

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ASSESS SEVERITY OF RISK

1. Differentiate between complicated and uncomplicated SAM by using Document 1: Case definition of SAM, to refer patients appropriately and ensure optimal care.
2. Uncomplicated SAM with low risk is suitable for Level 1 hospital care.
3. Complicated SAM with high-risk and infants < 6 months with SAM will require Level 3 hospital care; whilst uncomplicated SAM with moderate risk will require level 2 hospital care.

MEDICAL INVESTIGATIONS

Perform Dextrostix test in outpatients/casualty and on admission on all patients.

Bloods: blood glucose (glucostix test on admission), electrolytes & urea, total protein, albumin; FBC; blood culture, CMP, CRP

Urine MCS (document urine dipsticks result in folder) and culture if UTI suspected;

Chest X-ray-AP and lateral

Mantoux and two gastric washings (if TB suspected), HIV test (all malnourished children).

LP if clinically indicated

STEP 1

Hypoglycaemia (Low blood sugar), Hypoglycaemia is a blood glucose <3mmol/L

PREVENTION

For children with normal blood glucose i.e. > 3 mmol

1. Feed stabilising feeds /F75 straight away i.e. on arrival at hospital and within 30 minutes after admission (use feeding chart to find amount to give) and then every 2 hours for first 48 hours and then every 3 hours, day and night.
2. Document time of first feed given.
3. Encourage mothers to stay with very ill children to watch for any deterioration, help feed and keep child warm.

WARNING SIGNS

1. Low temperature (hypothermia) noted on routine check.
2. Child feels cold.
3. Child becomes drowsy or lethargic.
4. Signs of Shock.
5. If blood sugar is low, monitor blood sugar every 30 minutes to 60 minutes and intervene accordingly.

IMMEDIATE ACTION

Check blood glucose immediately and record.

1. If unable to drink, depressed level of consciousness, or convulsing and blood sugar is below 3mmol/L:-

Give 5ml/kg of sterile 10% dextrose IV or IO: prepare 1ml/kg 50% dextrose mixed with 4ml/kg sterile water or use 5ml/kg NNL. Follow with maintenance IV 1/2DD (if shocked) or NG feeds or dextrose containing fluid. Monitor response to treatment every 30 minutes

If alert and able to drink and blood sugar is below 3mmol/L:-

Give oral/NG feed or give 10% glucose (50ml) orally or by NGT. To prepare 10% glucose solution: mix 10ml 50% dextrose with 40ml sterile water, or sugar solution (1 rounded teaspoon sugar in three tablespoons of plain water) If 10% glucose is not available, give sugar solution or stabilising feed/F75 rather than wait for glucose. Test again 30 minutes after treatment. If blood sugar is still low, repeat oral 50ml 10% glucose or sugar solution. Consider putting up a short IV line.

Recheck blood glucose after 30 minutes, monitor hourly until 3 consecutive values >3mmol/l then 3-4 hourly

If blood sugar is persistently low, review feed and look for infections.

Feed 2-hourly (12 feeds in 24 hours). Start straightaway.

Commercial stabilising feed/F75	No or mild oedema	With severe oedema
	130 ml/kg/d	100 ml/kg/day

Give via Nasogastric tube (NGT) if oral intake is poor

The specialised commercial formula (F75), containing 75kcal/100ml and 0.9g protein/100ml is recommended. Where the commercial stabilising feed (F75) is not readily available, refer to Document 5: Feeding regimen for equivalent low protein products [See Point 7 Stabilisation feeding]

Check blood glucose 3-4 hourly until stable for first 48 hours

STEP 2

Hypothermia (Low temperature) Hypothermia is a underarm/axillary temperature <35 degree celsius

PREVENTION

For all children:-

- 1 Feed straight away and then every 2-3 hours, day and night.
2. Keep warm. Let mother sleep with child to keep child warm. Cover with a blanket.
3. Keep room warm, no draughts.
4. Keep bedding/clothes dry. Dry carefully after bathing (do not bathe if very ill). Avoid early morning bathing in cold weather.
5. Avoid exposure during examinations, bathing.
6. Ensure temperature is monitored four hourly.

WARNING SIGNS

1. Cold extremities
2. Inactive, lethargic
3. Poor appetite

NOTE: Hypothermia in malnourished children often indicates coexisting hypoglycaemia and serious infection.

IMMEDIATE ACTION

Take temperature on admission (Digital if available or ensure non-digital thermometer is well shaken down).
Check temperature 3-4 hourly.

If the temperature is below 36.5 degree celsius

1. Feed straight away (or start rehydration if children have diarrhoea with dehydration).
2. Active rewarming Re-warm. Put the child on the mother's bare chest (skin to skin contact) and cover them, OR clothe the child including the head, cover with a warmed blanket and place a heater or lamp nearby.
3. Feed 2-hourly (12 feeds in 24 hours).

Monitor during re-warming

- Take temperature every two hours: stop re-warming when it rises above 36.50C
- Take temperature every 30 minutes if heater is used because the child may become overheated.

STEP 3

Some or Severe Dehydration (without shock) (too little fluid in the body)

PREVENTION

When a child has watery diarrhoea feed straightaway and give 10ml/kg ORS between feeds to replace stool losses.

As a guide:

1. Give 50-100ml after each watery stool for children <2years; and
2. Give 100-200ml to older children.

Continue feeding, including breastfeeding.

WARNING SIGNS

Profuse watery diarrhoea, sunken eyes, slow skin pinch, absent tears, dry mouth, very thirsty, reduced urine output, sunken fontanelle, rapid pulse and respiration.

IMMEDIATE ACTION

DO NOT GIVE IV FLUIDS EXCEPT IN SHOCK

See Emergency Treatment wall chart for treating shock

If child is shocked:

Use shock protocol* (Addendum 1) Start with 10ml/kg normal saline or ringers lactate bolus

If dehydrated (not in shock):

1. Give ORS (orally or by Nasogastric tube) 5 ml/kg every 30 minutes for first 2 hours using frequent small sips. Show the caregiver how to give ORS with a cup and spoon. If child vomits wait 10 minutes and then continue more slowly.

2. Continue with 10ml/kg/ hour up to 10 hours (remember to prescribe 2-hourly feeds in addition).

3. Stop ORS if there are signs of over-hydration.

4. Encourage caregiver to continue feeding the child, especially if breastfeeding.

Monitor during rehydration for signs of over-hydration at least hourly.

- increasing pulse and respiratory rate
- increasing oedema and puffy eyelids

Review at least hourly general condition, capillary filling time, level of consciousness, skin turgor, sunken eyes, respiratory rate, abdomen, if passing urine and number/quality of stools.

If shock redevelops, then treat for shock (emergency wall chart)

If dehydration is improving- continue for up to 10 hours

If there is no dehydration go to prevention 10ml/kg ORS orally after each loose stool.

If dehydration is not improving consider IV fluids with great care.

STEP 4

Electrolyte imbalance (Too little potassium, magnesium, phosphate and too much sodium in body tissue)

PREVENTION

1. Do not add salt to food.
2. Use standard low osmolarity ORS and stabilising FEED/F75 formula as these are low in sodium.
3. Do not treat oedema with diuretics. Give extra potassium and magnesium (either as CMV in feeds or as a supplement).

WARNING SIGNS

Oedema develops or worsens, poor appetite and apathy

IMMEDIATE ACTION

Give daily: extra potassium, magnesium and phosphate

For potassium: 4mmol/kg/day. KCl weight < 10 kg 250 mg; weight > 10kg: 500mg Give 8hrly orally until the oedema has resolved.

For magnesium: Mg 0.4 - 0.6 mmol/kg/day or Mg Cl 50mg/kg/ day

For phosphate: Phosphate 1-2 mmol/kg/day if low (Phosphate Sandoz effervescent tablet per 16ml water gives 1 mmol/ml); can however cause or exacerbate diarrhoea.

STEP 5

Infections

1. Good nursing care.
2. Reduce overcrowding if possible.
3. Wash hands before preparing feeds and before and after dealing with any child.
4. Give measles vaccine to unimmunised children over 6 months of age.
5. If possible, protect these children from children admitted with severe infection by having a separate room/ward for SAM children.
6. Follow guidelines for “safe preparation, storage and handling of feeds.

PREVENTION

NOTE: The usual signs of infection, such as fever, are often absent so assume all severely malnourished children have infection and treat with antibiotics. Hypothermia and hypoglycaemia are signs of severe infection.

NOTE: ensure all doses are given. Give them on time.

IMMEDIATE ACTIONS

Starting on the first day, give antibiotics to all children.

1. If the child is severely ill (apathetic, lethargic) or has complications (hypoglycaemia, hypothermia, raw skin/fissures, meningitis, respiratory tract or urinary tract infection) give IV Ceftriaxone 100mg/kg/day for 5 days
2. If the child has medical complications but not seriously ill, give IV Ampicillin: 50mg/kg IV 6-hourly for 5 days AND Gentamicin: 7.5mg/kg IV once daily for 5 days. If a child fails to improve after 48 hours, search for new infection, then change to Ceftriaxone 100mg/kg daily IM/IV for 5-7 days (or guided by local microbiological flora).

If the child does not improve after 48-72 hours, then change antibiotics and refer to higher level of care.

3. If the child has no medical complications, give antibiotics orally Cefuroxime 15mg/kg/dose 12-hourly for 5 days or Augmentin 30mg/kg/dose 8 hourly(if no diarrhoea) or Amoxicillin 30mg/kg 8-hourly for 5 days

NOTE: Avoid steroids as these depress immune function. Give measles vaccine if due. Continue use of cotrimoxazole to prevent PCP pneumonia if indicated.

4. If the child has diarrhoea, add Metronidazole 7.5mg/kg/dose 8-hourly

5. Treat for intestinal infestation (parasitic worms) once stable:

1-2 yrs old or < 10kg Mebendazole 100mg po bd for 3 days

> 2 yrs and > 10kg Mebendazole 500mg po single dose

Investigate for TB. Do Tuberculin Skin Test and read it within 48 hours. Record the findings.

Counsel and Test for HIV. Record the findings.

STEP 6

Micronutrient Deficiencies

Vitamin	Schedule	Dose
Folic acid	Daily	2.5mg
	On discharge	1 month supply sent home (if discharged on RuTF no need for additional Folic Acid)
Vitamin A	<p>Day 1 to all malnourished children unless there is definitive evidence that a dose has been given during the past month.</p> <p>Repeat dose on Day 2 and day 14 if there are any clinical signs of vitamin A deficiency (e.g. night blindness, conjunctival xerosis with Bitot's spots, corneal xerosis or ulceration, or keratomalacia)</p> <p>Children with severe measles should receive Vitamin A on days 1,2 and 14</p>	<p><6 months 50 000 IU</p> <p>6 - 11 months 100 000 IU</p> <p>12-59 months 200 000 IU</p>

Multi-vitamin	Give multivitamin syrup - without iron, daily.	<p>0-1months: multivit syrup e.g. Kiddy-vit 0.3 ml per day</p> <p>1-12 months: multivit syrup e.g. Kddy-vit 0.6 ml per day</p> <p>>1 year multivit syrup 5 ml daily (if stabilising FEED/F75 is used no need for multi-vit)</p>
Iron	Do not give iron during the initial/stabilisation phase of treatment even if aenamic as it can have toxic effects and may reduce resistance to infection.	
	In rehabilitation phase for children with anaemia start iron when oedema has resolved and the child is gaining weight	Elemental iron 3mg/kg/day
	<p>Very severe anaemia</p> <p>Most children with SAM tolerate a low haemoglobin but if the Hb concentration is very low (less than 4-5g/dl) the child may be symptomatic with heart failure (tachycardia, gallop,</p>	

	hepatogaly, respiratory distress). These children, and those with anaemia and severe pneumonia on oxygen will need a cautious blood transfusion. Give 10 ml/kg of packed red cells slowly over 4 hours. Give 1mg/kg Lasix IV half way through or at the end of the transfusion. Another 10ml/kg can be given 12-24 hours later if required. Monitor closely for fluid overload during transfusion	
Zinc	Daily (Zinc sulphate/Zinc picolinate)	< 10kg:10 mg daily > 10kg:20 mg daily

STEP 7

7. Stabilisation feeding (stabilisation Phase)

Re-establish breastfeeding OR feed with commercial stabilising feed/F75 as soon as possible after admission. The usual fluid requirement is F75 130ml/kg/day or 100 ml/kg/day if very oedematous (3+) or unstable (risk of re-feeding syndrome and fluid shifts). Solids should not be given for at least the first 72 hours. Consult daily with dietician if available.

If replacement fed, give orally or via NGT.

- Where the commercial stabilising feed (F75) is not readily available, refer to Document 5: Feeding regimen for equivalent low protein products
- Aim for 100 kcal/kg/day and protein of 1-1.5 g/kg/day
- Low osmolarity, low lactose feeds

Those starting at lower volume can be increased by 10-20ml/kg/day if stable/no excessive weight gain

3. Frequency of *feeds: Give 8-12 feeds over 24 hours.

- Day 1-2: 2 hourly feeds; 12 feeds over 24 hours;
- Day 3-5 and onwards: 3 hourly feeds; 8 feeds over 24 hours;
- *See document five for feeding regimen

4. Keep a 24-hour intake chart. Measure feeds carefully. Record leftovers. If the intake is <80% of the total prescribed intake for 2 to 3 consecutive feeds, insert Nasogastric tube for feeding. If in doubt check feeding chart for intakes.

5. Weigh daily and plot weight on RtHB/WHO growth charts; calculate weight gain.

6. A gradual transition helps to prevent re-feeding syndrome.

STEP 8

8. Transition feeding and Catch-up growth rehabilitation phase

1. If child is breastfed, encourage mother to continue breastfeeding. If replacement fed: Transfer to catch-up formula(F100) as soon as appetite has returned (usually within one week) and/or oedema is lost or is reduced, initiating at 150kcal//kg/day and 2-4gprotein/kg/day.

- For 2 days, replace stabilising FEED/F75 with same amount of F100. (F100: 100 kcal, 2.9g protein per 100ml).
- On day 3 increase each feed by 10ml until it reaches 150-180ml/kg/day until some feed remains.
- Careful build up to 200 kcal/kg/day and protein 4-6 g/kg/day Monitor renal function carefully.

Give 8 feeds over 24 hours(3-4 hourly). As the child is eager to eat, progress to five feeds of F 100 and 3 specially modified family meals, high in energy and protein. Ready-to-use Therapeutic Food(RuTF) may be introduced and given at discharge for catch-up growth.

Consult daily with dietician if available

2. To ensure rapid weight gain, encourage the child to eat as much as possible. If the child is finishing everything, offer more and increase subsequent feeds. Make sure that the child is actively fed. Involve the mother/caregiver in the feeding all the time.

3. Weigh daily, plot weight and record intake daily: weight gain should exceed 10 g/kg/day Use daily weight chart for recording and monitoring weight changes.

4. Failure to maintain catch-up growth may indicate an undiagnosed infection (TB, HIV,UTI) or inadequate intake, re-investigate.

STEP 9

9. Loving care, play and stimulation

1. Provide tender loving care and a stimulating environment
2. Help and encourage mothers to comfort, feed, bathe and play with their children.
3. Involve mother/caregiver in all the play/stimulation exercises.
4. Give 15-30 minutes of structured play daily when the child is well enough. (Involve Occupational Therapist and/or physiotherapist for structured play, if available or organise in the ward.)

STEP 10

10. Preparation for follow-up after discharge

Discharge Criteria: Discharge when there are signs of improvement: Good appetite, infection resolved, oedema resolved AND consecutive weight gain for 5 days Prior to Discharge ensure these are completed:

1. Investigate for TB. Careful history for contacts. Repeat Tuberculin Skin Test if initial response was negative, and read it within 48 hours. Record the findings. Do CXR.
2. Ensure counselling and Test for HIV was conducted. Record the findings.

3. Involve mother in the discharge process and follow-up plans. Obtain information on family background and socio-economic status. Refer all children to Social Services (SASSA, Social Development, Home Affairs) and/or hospital social workers.

4. Give health and nutritional education. Issue mother/caregiver with the Family Booklet for Child Health. Share educational messages about the child and self or example, Family Practices booklet containing information on when to return urgently to clinic, hygiene, infant feeding and complementary feeding advice, stimulation, family planning, HIV, immunisation, role of male partner). Work with Dietician to counsel mothers/caregivers on how to modify family foods, how often to feed and how much to give.

5. Register child on the Severe Acute Malnutrition Inpatient care register. Ensure the child is counted onto the provincial information system admissions, discharges and/or deaths tally sheet.

6. Establish a link with local PHC clinic and family's local Community Care Givers (CCGs) for home follow-up as they are a high-risk group.

7. Prepare a Discharge Summary and write a brief clinical summary in RTHB.

8. Send a NTP referral letter to the local PHC clinic. Ensure child is enrolled on nutrition therapeutic programme at local clinic or child returns to hospital outpatient in one week.

SWAZILAND HEALTH LABORATORY SERVICES

RFMH Laboratory

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SPECIMEN COLLECTION AND TRANSPORT

Purpose

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Equipment

Procedure

General Precautions

Safety and Infection Control

Troubleshooting Guidelines

Specimen Transport To The Laboratory

Co-Applicable Quality Management Documents

PURPOSE

This document describes the procedure followed by phlebotomists and technologists for proper specimen handling, i.e. collection and subsequent transport to the laboratory.

APPLICATION SCOPE

This procedure is to be used and followed by all sites and clinics which collect specimens to be sent to the laboratory for analysis.

PERSONNEL RESPONSIBILITY

It is the responsibility of the laboratory to ensure that staff at the sites and clinics are trained and are competent on this procedure. Adherence to this SOP is the responsibility of every person performing phlebotomy procedures or transporting specimens from clinics/sites to the laboratory.

EQUIPMENT

The following are needed for routine venipuncture:

Evacuated collection tubes - The tubes are designed to fill with a predetermined volume of blood by vacuum. The rubber stoppers are colour-coded to the additive that the tube contains. Various sizes are available. Blood should NEVER be poured from one tube to another since the tubes can have different additives or coatings (refer to Appendix 1).

Needles - The gauge number indicates the bore size: The smaller the gauge number, the larger the bore of the needle.

Needles are available for evacuated systems and for use with a syringe, single draw or butterfly system.

Holder/adapter - use with the evacuated collection system.

Tourniquet - Should be wiped off with alcohol and replace frequently.

Alcohol wipes - saturated with 70% isopropyl alcohol.

Povidine-iodine wipes/swabs - used if blood culture is to be drawn.

Gauze sponges - for application on the site from which the needle is withdrawn.

Adhesive bandages/tape - protects the venipuncture site after collection.

Needle disposal unit - needles should be placed in a sharps container immediately after their use. They should never be broken, bent, or recapped.

Gloves can be made of latex, rubber, vinyl, etc; worn to protect the patient and the phlebotomist.

Syringes - may be used in-place of the evacuated collection tube system for special circumstances.

PROCEDURE

Proper specimen collection and handling is an integral part of obtaining a valid and timely laboratory test results. Specimens must be obtained using proper phlebotomy techniques, collected in the proper container, correctly labelled and promptly transported to the laboratory.

BLOOD COLLECTION

Blood collection tubes with anticoagulant should be inverted several times as soon after collection as possible to prevent clotting. All blood collection tubes must be filled to the line in order to prevent dilution of blood components. Tubes with anticoagulant improperly filled will be rejected.

Deliver samples to the laboratory promptly. Valid measurement of analytes in serum or plasma requires prompt separation from the blood cells and analysis in the laboratory. Estimates of the level of biochemical constituents in the serum or plasma are different from their levels in whole blood. This is because many of the chemical substances are present in different concentrations in the plasma and the blood cells. It is the concentration in plasma or serum which changes in disease and can be used as an aid for diagnosis.

Venipuncture

Several essential steps are required for every successful collection procedure:

Identify the patient

Assess the patient's physical disposition (i.e. diet, exercise, stress, basal state)

Check the requisition form for requested tests, patient information, and any other special requirements.

Select a suitable site for venipuncture.

Prepare the equipment, patient and venipuncture site.

Perform the venipuncture.

Collect the sample in the appropriate container.

Assess the need for the sample recollection and/or rejection.

Label the collection tubes at the drawing area.

Promptly send the specimens with the requisition forms to the laboratory.

Patient identification

To provide high quality patient care, it is the policy of CL to assure positive identification. Therefore it is important to identify the patient prior to sample collection. Greet the patient and identify yourself and indicate the procedure that will take place. Proper patient identification is MANDATORY. Verify patient's initials and the patient identification (PID) number with that on the request form. DO NOT prelabel the specimen container with the patient information prior to sample collection.

Requisition form

A requisition form must accompany each sample that is submitted to the laboratory. This requisition form must contain the proper information in order to process the specimen. The essential elements of the requisition are:

Patient's initials

Unique patient identification number (PID/BID)

Date and time of collection

Initials of the person collecting the sample (phlebotomist)

Patient sex and date of birth

Initials of the clinician requesting the test

Billing information

Test to be performed

Specimen container

A properly labelled sample is essential so that the test results match the patient. The key elements in labelling are:

Patient's initials

Unique patient identification number (PID/BID)

Letter code of eth test requested

Order of draw

Blood collection tubes must be drawn in a specific order to avoid contamination by additives between tubes. The recommended order of draw is:

1) Blood culture tube (yellow-black top)

2) Non-additive tube (red-top or SST)

3) Coagulation tube (light blue top). If a routine coagulation assay is the only test ordered, then a single light blue top tube may be drawn. If there is a concern regarding contamination by tissue fluids or thromboplastins, then one may draw a non-additive tube first, and then the light blue top tube.

Last - additive tubes in this order:

a) SST (red-grey, or gold top). Contains a gel separator and clot activator.

b) Sodium-heparin (dark green top).

c) Plasma separating tube (PST) (light green stopper). Contains lithium heparin anticoagulant and a gel separator.

d) EDTA (lavender/purple top).

e) ACDA or ACDB (pale yellow top). Contains acid-citrate-dextrose.

f) Oxalate/fluoride (light grey top).

Note: Tubes with additives must be thoroughly mixed. Erroneous test results may be obtained when the blood is not thoroughly mixed with the additive.

Note: For plastic tubes, order of draw for non-additive and coagulation tubes is reversed.

Venipuncture site selection

Although the larger and median cubital and cephalic veins of the arm are used most frequently, wrist and hand veins are also acceptable for venipuncture.

Certain areas are to be avoided when choosing a site:

Extensive scars from burns and surgery - it is difficult to puncture the scar tissue and obtain a specimen.

The upper extremity on the side of a previous mastectomy - test results may be affected because of lymphedema.

Hematoma - may cause erroneous test results. If another site is not available, collect the specimen distal from the hematoma.

Intravenous therapy (IV)/blood transfusions - fluid dilute the specimen, so collect from the opposite arm if possible.

Otherwise, satisfactory samples may be drawn below the IV by the following procedures:

Turn off the IV for at least 2 minutes before venipuncture.

Apply tourniquet below the IV site. Select a vein other than the one with the IV.

Perform the venipuncture. Draw 5ml of blood and discard before drawing the specimen tubes for testing.

Cannula/fistula/heparin lock - hospitals have special policies regarding these devices. In general, blood should not be drawn from an arm with a fistula or cannula without consulting the attending physician.

Oedematous extremities - tissue fluid accumulation alters test results.

Procedure for vein selection

Palpate and trace the path of veins with the index finger. Arteries pulsate, are more elastic, and have a thick wall. Thrombosed veins lack resilience, feel cord-like and roll easily.

If superficial veins are not readily apparent, you can force blood into the vein by massaging the arm from the wrist to the elbow, tap the site with index and second finger, apply a warm, damp wash cloth to the site for 5 minutes, or lower the extremity to allow veins to fill.

Performance of a venipuncture

Approach the patient in a calm friendly manner. Provide for their comfort as much as possible, and gain the patient's cooperation.

Identify the patient correctly.

Properly complete the appropriate requisition forms

Verify the patient's condition. Fasting, dietary restrictions, medications, timing, and medical treatment are all of concern and should be noted on the lab requisition form.

Position the patient. The patient should sit on a chair, lie down or sit up in bed

Hyperextend the patient's arm and apply a tourniquet 3 - 4 inches above the selected puncture site. Do not place too tightly or leave on for more than 2 minutes.

The patient should make a fist without pumping the hand.

Select the venipuncture site.

Prepare the site using an alcohol swab. Cleanse in a circular manner, beginning at the site and working outward. Allow to air-dry.

Grasp the patient's arm firmly using your thumb to draw the skin taut and anchor the vein. Swiftly insert the needle through the skin and into the lumen of the vein. Avoid trauma and excessive probing.

When the last tube to be drawn is filling, remove the tourniquet.

Remove the needle from the patient's arm using a swift backwards motion.

Press down on the gauze once the needle is out of the arm, applying adequate pressure to avoid formation of a hematoma.

Dispose of contaminated materials in designated containers.

Label and mix all appropriate tubes immediately.

Deliver specimens and requisition forms to the laboratory promptly.

Performance of a finger stick

Follow the procedure so outlined above for greeting and identifying the patient. As always, fill out the appropriate requisition forms.

Verify the patient's condition. Fasting, dietary restrictions, medications, timing, and medical treatment are all of concern and should be noted on the lab requisition form.

Position the patient. The patient should sit on a chair, lie down or sit up in bed. Hyperextend the patient's arm.

The best locations for fingersticks are the 3rd and 4th fingers of the non-dominant hand. Do not use the tip or centre of the finger. Avoid the side of the finger where there is less soft tissue, where vessels and nerves are located, and where bone is closer to the surface. The index finger tends to have thicker, calloused skin. The fifth finger tends to have less soft tissue overlying the bone. Avoid puncturing a finger that is cold or cyanotic, swollen, scarred, or covered with a rash.

Using a sterile lancet, make a skin puncture just off the centre of the finger pad. The puncture should be made perpendicular to the ridges of the fingerprint so that the drop of blood does not run down the ridges.

Wipe away the first drop of blood, which tends to contain excess tissue fluid.

Collect drops of blood into a collection device by gently massaging the finger. Avoid excessive pressure that may squeeze tissue fluid into the drop of blood.

Cap, rotate and invert the collection device to mix the blood collected.

Have the patient hold a small gauze pad over the puncture site for a couple of minutes to stop the bleeding.

Dispose of contaminated materials in designated containers.

Label all appropriate tubes at the collection area.

Deliver specimens promptly to the laboratory.

Blood collection on babies

The recommended location for blood collection on a newborn baby or infant is on the heel.

Prewarming the infant's heel (42°C for 3-5 minutes) is important to obtain capillary blood gas samples. Warming also greatly increases the flow of blood for collection of other specimens. However, do not use too high a temperature warmer, because baby's skin is thin and susceptible to thermal injury.

Clean the site to be punctured with an alcohol sponge. Dry the cleaned area with a cotton sponge. Hold the baby's foot firmly to avoid sudden movement.

Using a sterile blood lancet, puncture the side of the heel. Do not use the central portion of the heel because the underlying bone, which is close to the skin surface, might be injured. Do not use a previous puncture site. Make the cut across the heel print lines so that a drop of blood can well up and not run along the lines.

Wipe away the first drop of blood with a piece of clean, dry cotton. Since newborns do not often bleed immediately, use gentle pressure or heavy massaging because the blood may become diluted with tissue fluid.

Fill the capillary tube(s) or micro-collection device(s) as needed.

When finished, elevate the heel, place a piece of clean, dry cotton to the puncture site, and hold it in place until the bleeding has stopped.

Be sure to dispose of the lancet in the appropriate sharps' container.

Dispose of other contaminated materials in appropriate waste containers.

Blood collection tubes

Blood obtained by venipuncture may be collected directly into tubes that have been pretreated with coagulants. The vacutainer[®] evacuated blood collection system (Becton-Dickinson Co., New Jersey) consists of the following:

An evacuated glass/plastic tube containing a premeasured vacuum to ensure that a specified volume of blood is drawn.

A sterile single-use blood collection needle suitable for drawing either single or multiple samples after venipuncture.

A specially designed holder which may be used optionally to secure the needle during venipuncture and insertion into the tube top.

The tubes are available in a variety of sizes and with a variety of additives. Tubes containing no anticoagulants are used for tests requiring serum. The stopper colour coding for the tubes is listed in Table 1. Powdered anticoagulants are utilised in most vacutainer tubes because liquid anticoagulants may dilute blood and affect results.

The recommended container should be used and transferring of specimen from one type of vacutainer to another is not allowed. Using the wrong container often leads to erroneous results

It is important to draw the correct amount of blood (fill the tube) to obtain the proper ratio of anticoagulant to blood.

01.6 GENERAL PRECAUTIONS

01.6.1 Avoid hemolysis

Red blood cells contain certain analytes in concentrations many times higher than in plasma. When red blood cells are hemolysed, there is a release of these analytes and dilution of the plasma results in erroneous laboratory values. Grossly hemolysed samples will be rejected for any analyte in the laboratory. A sample visibly hemolysed will be rejected for the following analytes:

Acid phosphatase

ALP (Alkaline phosphatase)

Amylase

ALT (Alanine transferase)

AST (aspartate aminotransferase)

Bilirubin

CK-MB (Creatine Kinase - myocardial tissue specific)

Glucose

Lipase

LDH (Lactate Dehydrogenase)

Phosphorus

Potassium

RPR (Rapid Platin Reagin)

VDRL (Venereal Diseases Reference Laboratory)

01.6.2 Hemolysis can be caused by:

Mixing additive tubes too vigorously or using rough handling during transport.

Drawing blood from a vein that has a hematoma.

Pulling back the plunger on a syringe too quickly.

Using a needle with too small a bore for the venipuncture.

Using too large a tube when using a small diameter butterfly needle.

Frothing of the blood caused by improper fit of the needle on a syringe.

Forcing blood from a syringe into an evacuated tube.

01.6.3 Prevent hematoma

Puncture only the uppermost wall of the vein.

Remove the tourniquet before removing the needle.

Use the major superficial veins.

Make sure the needle fully penetrates the uppermost wall of the vein (Partial penetration may allow blood to leak into the soft tissue surrounding the vein by way of the needle bevel).

Apply pressure to the venipuncture site.

01.6.4 Avoid clotted samples

Inadequate mixing of the vacutainer tube as soon as possible after phlebotomy will result in the blood not mixing with the anticoagulant. By gently inverting the vacutainer 5-10 times, the blood will mix and clotting will NOT occur.

01.6.5 Insufficient specimen quantity

If the vacutainer is allowed to fill completely, there will be enough specimen to complete most tests. Vacutainer tubes half-filled or less than half filled may result in the lab requesting another sample to be drawn.

01.6.6 Avoid prolonged tourniquet application

Primary effect is hemoconcentration of non-filterable elements (i.e. proteins). The hydrostatic pressure causes some water and filterable elements to leave the extracellular space.

Significant increases can be found in total protein, aspartate aminotransferase (AST), total lipids, cholesterol, and iron.

Affects packed volume and other cellular elements

01.6.7 Hemoconcentration is an increased concentration of larger molecules and formed elements in the blood and may be caused by:

Prolonged tourniquet application (more than 2 minutes).

Massaging, squeezing or probing a site.

Long-term IV therapy.

Sclerosed or occluded veins.

01.6.8 Indwelling lines or catheters:

Potential source of test error.

Most lines are flushed with a solution of heparin to reduce risk of thrombosis.

Discard a sample at least three times the volume of the line before a specimen is obtained for analysis.

SAFETY AND INFECTION CONTROL

Because of contact with sick patients and their specimens, it is important to follow safety and infection control procedures.

Protect yourself

Practice universal precautions

Wear gloves and a lab coat or gown when handling blood/body fluids.

Change gloves between patients and whenever they are contaminated.

Wash hands frequently.

Dispose of items in appropriate containers.

Dispose of needles immediately upon removal. Do not bend, break, recap or re sheath needles to avoid accidental needle puncture or splashing of contents.

Clean up any blood spills with a disinfectant such as freshly made 0.5% bleach followed by 70% ethanol.

If you stick yourself with a contaminated needle:

Remove gloves and dispose of them properly.

Squeeze puncture site to promote bleeding.

Wash the area well with soap and water.

Record the patient's name and PID.

Follow the institution's guidelines regarding treatment and follow-up (Post-exposure prophylaxis procedure).

Protect the Patient

Place blood collection equipment away from patients, especially children and psychiatric patients.

Practice hygiene for the patient's protection. When wearing gloves, change them between each patient and wash your hands frequently. Always wear a clean lab coat or gown.

Hazardous conditions, practices, injuries or accidents must be immediate and always reported to a supervisor and/or safety officer for follow-up and assurance that appropriate medical attention is received if needed. Failure to do so could put other workers and patients in a potentially harmful situation. Reporting all unsafe conditions and accidents to the appropriate party is an ethical and moral job responsibility for all professionals.

TROUBLESHOOTING GUIDELINES

If An Incomplete Collection Or No Blood Is Obtained:

Change the position of the needle, move it forward (it may not be in the lumen), or move it backwards (it may have penetrated too far).

Adjust the angle (The bevel may be against the vein wall).

Loosen the tourniquet; it may be obstructing blood flow.

Try another tube; there may be no vacuum in the one being used.

Re-anchor the vein; veins sometimes roll away from the point of the needle and puncture site.

If Blood Stops Flowing Into the Tube

The vein may have collapsed; re-secure the tourniquet to increase venous filling. If this is not successful, remove the needle, take care of the puncture site and redraw.

The needle may have pulled out of the vein when switching tubes. Hold equipment firmly and place fingers against patient's arm, using the flange for leverage when withdrawing and inserting tubes.

Problems Other Than Incomplete Collection A hematoma forms under the skin adjacent to the puncture site - release the tourniquet immediately and withdraw the needle. Apply firm pressure.

The blood is bright-red (arterial), rather than venous - Apply firm pressure for more than 5 minutes.

TRANSPORT OF SPECIMENS TO THE LABORATORY

All laboratory specimens should be treated as though infected with blood borne or other pathogens.

The clinical staff at the sites is responsible for the phlebotomy and the appropriate arrangement of samples onto a specimen rack. The clinical staff is also responsible for the transfer of samples into an appropriate cooler box which must be labelled 'biohazard'.

Specimen should be divided and put in different cooler boxes according to the required temperature for each test (Refer to Appendix 2 for guidance).

The samples may only be handed over to the driver after they are securely placed in the cooler box and the cooler box is securely closed.

The driver receiving the cooler box should ensure that he/she is wearing protective equipment; one hand should be gloved (to hold the cooler box) and the other ungloved to open doors. The glove should be removed during driving of the vehicle. However, on arrival at the lab, the driver should resume the one handed glove method as he/ she delivers the samples to the sample receiving area.

Spills should be wiped up immediately with disposable towels, whilst wearing gloves, and then the surface wiped with disposable towels using a full strength disinfectant (3.5% bleach followed by 70% alcohol). Spill kits should be directly available for all drivers.

All spills and exposures should be reported to the Safety Officers.

CO-APPLICABLE QUALITY MANAGEMENT DOCUMENTS

Procedure 002/PR-01 - Daily Specimen Reception and Processing Procedure

Procedure 009/PL-02 - Waste Disposal Policy

Procedure 009/PL-01- Universal Precautions Policy

Procedure 009/PR-02 - Decontamination of spills

Procedure 009/PR-04 - Decontamination of Work surfaces and Biosafety Cabinets

Procedure 009/PL-03 - BHP PEP Policy

Appendix 1: Tube types and their recommended uses

Top colour	Additive	Mode of action	Uses
Red	None	Blood clots and the serum is separated by centrifugation	Chemistries, Immunology and serology, blood bank (cross match)
Gold	None	SST contains a gel at the bottom to separate from serum on centrifugation	Chemistries, Immunology and Serology
Light green	Lithium Heparin	Anticoagulates with lithium heparin, plasma is separated with PST gel at the bottom of the tube	Chemistries

Red-grey (tiger)	Serum separating tube with clot activator	Forms clot quickly and separates the serum with the SST gel at the bottom of the tube	Chemistries
Purple	EDTA liquid	Forms calcium salts to remove calcium	Haematology (CBC) and blood bank (cross match); requires full draw- invert eight times to prevent clotting and platelet clumping
Light blue	Sodium citrate	Forms calcium salts to remove calcium	Coagulation tests (protime and prothrombin time), full draw required
Dark Green	Sodium-heparin or lithium heparin	Inactivates thrombin and thromboplastin	For lithium level, use sodium-heparin. For ammonia level, use sodium or lithium heparin
Dark Blue	Sodium EDTA	Tube designed to contain no contaminating metals	Trace element testing (zinc, copper, lead, mercury) and toxicology

Light grey	Sodium fluoride and potassium oxalate	Antiglycolytic agent preserves glucose up to 5 days	For lithium level, use sodium-heparin. Glucoses. Requires full draw (may cause hemolysis if short draw)
Top Colour	Additive	Mode of action	Uses
Yellow	ACD (acid-citrate-dextrose)	Complement inactivation	HLA tissue typing, paternity testing, DNA studies
Yellow-black	Broth mixture	Preserves viability of microorganisms	Microbiology - aerobes, anaerobes, fungi
Black	Sodium citrate (buffered)	Forms calcium salts to remove calcium	Westergren Sedimentation Rate. Requires full draw
Orange	Thrombin	Quickly clots blood	STAT serum chemistries
Brown	Sodium-Heparin	Inactivates thrombin and thromboplastin	Serum lead determination

RFMHL C6 SP 07/F01

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Appendix 2: General Sample Criteria for CL

	Requirements				
Test	Tube Type	Tube volume	Specimen condition	Maximum delivery time/ temperature	Storage before Testing
CD4 Cell Count	Vacutainer with EDTA additive (purple top)	Minimum 0.5ml	Neither clotted nor haemolysed	24 hours/ room temperature	48 hours/ room temperature

Hepatitis B/C Syphilis Serology	Plain (red top with no additive) or yellow top with SST gel	Minimum 3.0ml	Not haemolysed	24 hours/ 4 °C	14 days/ 4 °C or below - 20°C
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Requirements					
Test	Tube Type	Tube volume	Specimen condition	Maximum delivery time/ temperature	Storage before Testing
Haematology	Vacutainer with EDTA additive (purple top)	Minimum Infants 0.5ml Adults 1.0ml	Not clotted Not haemolysed	24 hours/ 4 °C	24 hours/ 4 °C

Chemistry Liver function Cardiac Kidney U/E	Blood in plain vacutainer; red top with no additive or yellow top with SST gel	Minimum Infant 0.5ml Adults 3.0ml	Not haemolysed	24 hours/ 4 °C	24 hours/ 4 °C
Chemistry Lactate	Blood in vacutainer with Potassium oxalate or sodium fluoride as additive (grey/ green top)	Minimum 3.0ml	Not clotted Not haemolysed	15 min/ ice or 2 hours/ room temperature if separated into plasma or 2 days/4-8°C	None

Chemistry Glucose	Blood in vacutainer with potassium oxalate or sodium fluoride as additive(grey top)	Minimum 3.0ml	Not clotted Not haemolysed	24 hours/ 4 °C	24 hours/ 4 °C
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Immunology Storage	Vacutainer with EDTA additive (purple top)	Minimum 5.0ml	Neither clotted nor haemolysed	6 hours/ 4 °C	-70 °C until tested
Viral Load Storage	Vacutainer with EDTA additive (purple top)	Minimum 5.0ml	Neither clotted nor haemolysed	6 hours/ 4 °C	-70 °C until tested

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Appendix 3: SOP Attestation Form

<p>Attestation Record (general staff SOP Review At least annually)</p> <p>{Please ensure that you have read and understood before signing}</p>		
Names	Signature	Date

RFMHL SBP 07

SOP FOR CULTIVATION OF BACTERIA ON MEDIA

SHLS

RFMHL SBP 07

SOP FOR CULTIVATION OF BACTERIA ON MEDIA

SHLS

SWAZILAND HEALTH LABORATORY SERVICES

RFMH Laboratory

Effective Date: 08/09/2014

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RFMHL Confidential Controlled Document

Title : **SOP FOR CULTIVATION OF BACTERIA ON MEDIA**

Document Number : **RFMHL SBP 07**

Version : **1**

Effective Date : **08 May 2018**

Written by : **Laboratory Quality Team**

Checked by : **Quality Officer** _____

Approved by : **Laboratory Manager** _____

Date of next review	Date reviewed	Reviewed by	Action
08 May 2019			

Record of Amendment (if applicable)			
Version No.	Date of Amendment	Description of Amendment	

Distribution		
Location:	Copy Number:	Responsible person

Purpose

For inoculating specimens onto culture media and sub-culturing from one medium to another in microbiological investigations

Responsible personnel

Technologist, Technician or Student Technologist

Safety

Personal protective equipment must be worn at all times.

Decontamination of the working area must be carried out per SOP

Any spillage occurring during sample receiving should be dealt with according to the laboratory health and safety guidelines.

Materials and equipment

Sterilised loops

Media plates

Bunsen burner/ Flame

Biosafety Cabinet

Permanent Marker

Pasteur pipettes

Sterile swabs

Paper Towel

Instrument for seeding media

This is selected according to the nature of the medium and inoculum. Platinum or nichrome wires of different gauges are used. Nichrome has oxidising properties and hence in some of the tests where this property of bacterium is to be tested (e.g. oxidase test), platinum wire, instead of nichrome should be used. This wire is sterilised by holding it vertically in the flame of the burner so that the whole length of wire becomes red hot. It is allowed to cool down before it touches any material suspected to be having bacteria to avoid the heat killing the organisms. Presterilized disposable loops are now available commercially. The wire can be used as a:

- Straight wire to stab the culture, picking of single colonies as well as for inoculating the liquid media,
- Thick wire which is useful for lifting the viscid material such as sputum, and
- Wire loop which is usually of 2 mm diameter is most useful of all inoculating wires. These are preferred to seed a plate of medium as the straight wire usually cuts the agar.

Process of seeding a culture plate

Whole plates, half plates or quarter plates can be used depending on the circumstances.

Flame wire loops by holding them loop end down in a Bunsen flame until the loop and entire wire reaches red heat. Place on a rack to cool before use. This should be conducted before and after use and between agar plates. It is usual to use two loops, to allow adequate cooling of one after flaming whilst the other is in use. Different disposable loops should be used for each plate. For semi quantitative analysis of urine the loop should not be flamed.

The inoculum from the clinical material or another plate is first spread out in the form of a primary inoculum which is also called as 'well-inoculum' or only 'well'. The successive series of strokes are

made with the loop sterilised between each sequence. At each step the inoculum is derived from the most distal part of the immediately preceding strokes so as to gradually reduce the number of bacteria. This helps in obtaining isolated colonies.

In an alternative plating procedure, one edge of a large loop is used to make a secondary well. The other edge is then used to make succession of strokes across the remaining unseeded area.

When the inoculum is small or the medium is selective it can be more heavily inoculated. Several loop-fulls of the specimen are used to spread the primary inoculum. After sterilising the loop, it is recharged by rubbing it over inoculum area and the plate is seeded in parallel strokes.

Seeding a liquid medium

If the tubes have got cotton plugs, the mouth of the tubes should be heated in flame before and after any handling of tube to prevent contamination from the rims of tubes getting into the medium. It is not required when metal caps and screw-capped tubes are handled. Incline the tube containing the liquid medium to 45° and deposit the inoculum on its wall above the surface of the liquid at its lower end. Return the tube to a vertical position. Now the inoculum shall be below the surface of the liquid.

Sub-culture from a solid medium to solid medium

Using a sterile wire or loop, a representative colony is touched and sub-cultured onto appropriate solid medium by touching the wire or loop onto the surface of the medium.

Important points about inoculation of culture media

- Aseptic technique is important to avoid contamination.

Aseptic technique

With the exception of urine specimens, caps and lids from containers should not be placed on the workbench, but retained in the hand whilst the sample is being processed, taking care not to contaminate the hand or cap. Caps and lids should be replaced as soon as possible.

If the work is carried out on the open bench, a Bunsen burner should be in close proximity to flame loops or wires.

When opening culture containers keep samples away from the face.

Aerosol production should be minimised by:

Opening the caps slowly as the contents are sometimes under pressure

Avoiding vigorous swirling or shaking of the sample prior to opening

Cooling loops that have been heated before use

Avoid expelling the last drop from a pipette

If forceps or scissors are used when handling specimens, they should be heated in a Bunsen flame and allowed to cool before use.

Specimen Processing

Primary Culture Methods

Swabs- plate culture

Initial inoculum should cover between a quarter and a third of the plate to be used. The swab should be rolled over the inoculation area to maximise transfer of organisms, taking care to avoid the edges of the plate. Inoculation of samples on to selective media such as Sabourauds agar when usually a quarter plates only will be used may not require spreading with a loop.

Swabs- liquid culture

Using an aseptic technique, remove the broth container cap, place the swab in the broth, break off or cut the swab- stick and replace the cap. The swab may be placed in the broth directly, or after inoculating solid culture media.

Fluid specimens and pus

Resuspend the centrifuged deposit of any fluid in approximately 0.5mL supernatant, then transfer to appropriate culture media using a sterile pipette. Thick pus may require inoculation with the aid of a swab or swabstick.

Urine- calibrated loop, surface streak method

Mix the urine gently to avoid foaming. Dip the end of a sterile calibrated loop (e. g. 1 μ L, 2 μ L or 10 μ L) to just below the surface of the urine and remove vertically, taking care not to carry over any urine on the shank.

Urine- Filter paper method

Dip the commercially prepared sterile filter paper strip into the urine up to the mark indicated. Remove excess urine by touching the side of the strip against the side of the container and allow the urine time to absorb into the strip before inoculating a CLED agar plate. Bend the inoculated end of the strip and press it flat against the agar for a few seconds. Several specimens may be inoculated on to one CLED agar plate using this technique, but it is important to ensure adequate spacing to minimise the potential risk of any antibacterial effect.

Tissue and Biopsy specimens

Homogenise tissue using using a sterile tissue grinder or a pestle and mortar, and inoculate 1 or 2 drops of the homogenate on to appropriate media. Tissue may also be cut or sliced with a sterile scalpel, or preferably, sterile scissors. Using sterile forceps smear the sliced portion directly on to the culture medium. If enrichment culture is performed, this should be inoculated with pieces of specimen that have not been spread over the surface of solid media to avoid possible contamination. All homogenisation and grinding procedures must be performed in a biosafety cabinet.

Sub-culture methods**Sub-culture of liquid media to solid or liquid medium**

Obtain samples for sub-culture using a sterile loop (1 μ L, 10 μ L, etc) or a plastic pipette. Immerse the loop into the fluid to be sub-culture, and remove carefully without allowing excess fluid to remain on the shank of the shank of the loop. Either inoculate the loopful of fluid on to an appropriate agar plate, streaking out for individual colonies. The use of a pipette is particularly recommended when sub-culturing organisms to multiple culture media.

Sub-culture from a solid medium to a liquid medium

Select a representative colony or colonies of the organism to sub-culture using a sterile wire or loop to transfer to an appropriate broth. Gently agitate before incubation to distribute the organisms throughout the broth.

Sub-culture from a solid medium to a solid medium

It is recommended that a sterile wire be used when dealing with mixed cultures to ensure the sampling of the single colonies. Select a representative colony or colonies of the organism to be sub-cultured using a sterile wire or loop, and sub-culture on to the appropriate medium by touching the wire or loop on to the surface of the agar and then plate out. The use of a densitometer or McFarland standards may be required to adjust inoculum density.

References

www.evaluations-standards.org.uk

Sudarshan K. and R.L. Ichhpujani, 2000. Guidelines on Standard Operating Procedures for Microbiology, New Delhi.

Annex 1: SOP ATTESTATION FORM

Attestation Record (general staff SOP Review At least annually)		
{Please ensure that you have read and understood before signing}		
Names	Signature	Date

SWAZILAND HEALTH LABORATORY SERVICES

RFMH Laboratory

Title : **SOP FOR ANTIMICROBIAL SUSCEPTIBILITY TESTING**Document number : **RFMHL SBP 08**Version : **1**Effective Date : **18 May 2018**

Written by : **Knowledge Denhere**Checked by : **Quality Officer** _____Approved by : **Laboratory Manager** _____

Date of next review	Date reviewed	Reviewed by	Action
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Effective Date: 08/09/2014

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08 May 2019			
Record of Amendment (if applicable)			
Version No.	Date of Amendment	Description of Amendment	

Distribution		
Location:	Copy Number:	Responsible person

Purpose:

To test the sensitivity of bacterial isolates to antimicrobial agents so as to guide patient therapy

Principle

Susceptibility testing is conducted for organisms whose response to antimicrobial agents cannot be predicted from knowledge of the organism identity.

Disc diffusion is the most commonly used method for determining antimicrobial susceptibility. It predicts susceptibility based on break points that correlate zones of inhibition with the minimum inhibitory concentrations.

The methods described here are based on those of Kirby-Bauer. They must be explicitly followed in order to obtain reliable and reproducible results.

Responsibilities:

Setting and reading of the tests shall be performed by a trained technician

The overall process shall be under the supervision of a microbiologist

Safety issues:

Observe standard precautions.

Equipment and materials:

Equipment

Incubator at 35 - 37°C

Inoculating loops (10µl)

Test tubes

Sterile cotton tipped swabs

Calibrated ruler (in mm)

Forceps

Bunsen burner

Refrigerator (2 - 8°C)

Comparator card

Culture media

Muller-Hinton agar

Muller-Hinton Broth

Haemophilus test medium (for Haemophilus spp)

GC agar (for *Neisseria gonorrhoeae*)

Muller-Hinton agar supplemented with 5% sheep blood (for *S. pneumoniae* and other Streptococci)

Reagents/supplies

0.5 McFarland standard

Antimicrobial discs (potency summarised in tables for the various categories of organisms)

Sterile normal saline

Control strains:

E.coli 25922

E.coli 35218 (for β -lactam-inhibitor combinations)

S. aureus ATCC 25923

E. faecalis 29212 (for HLAR testing for *Enterococcus*)

H.influenzae 49247 (Ampicillin resistant β -lactamase negative)

H.influenzae 49766 (Ampicillin sensitive for control of β -lactam)

Klebsiella pneumoniae 700603 (Control for ESBL tests)

Neisseria gonorrhoeae 49226

Pseudomonas aeruginosa 27853

Streptococcus pneumoniae 49619

Procedure:

Preparation of inoculum:

Pick 3 - 5 discrete colonies from an 18 - 24 hour old culture using a loop

Transfer into a tube containing 4 - 5 ml of sterile normal saline and emulsify.

Adjust the turbidity of the suspension so that it matches that of the 0.5 McFarland standard by adding more sterile saline or more of the growth.

(To do this, compare the suspension with the McFarland standard against a card with a white background and contrasting black lines in the presence of adequate light)

Note

Always use well isolated/discrete colonies.

(In case the colonies are not discrete, first prepare a purity plate on a non-inhibitory medium before performing susceptibility testing)

Use Cultures that are not more than 18 - 24 hours old. Sub-culture for fresh growth if the cultures are too old.

Use the suspension within 15 minutes of adjusting the turbidity standard

Inoculation of plates:

Label well dried plates of Muller-Hinton agar with the number of the specimen and identification of the isolate

Dip a sterile cotton tipped swab into the adjusted suspension of the isolate

Rotate the swab several times, pressing it firmly against the inside wall of the tube above the fluid level to drain excess inoculum from the swab

Streak the swab over the entire surface of the agar.

Rotate the plate through about 60° and repeat the streaking. Do this twice.

Swab the rim of the agar as the final step in streaking

In case the surface of the plate appears wet after the streaking, leave the plate on the bench (agar side down) with the lid slightly ajar for 3 - 5 minutes. (In any case not more than 15 minutes)

Application of discs:

Place the appropriate discs on to the agar surface using a pair of forceps

(tables 6.5 - 6.16 for selection of antimicrobial agents for various organisms)

Space the discs so that they are at least 24 mm from each other. No more than five discs should be placed on each 100mm plate or 12 discs on 150mm plates.

Press the disc down to ensure complete contact with the agar

Incubate the plates inverted in an incubator at 35°C within 15 minutes of placing the discs on to the plate.

(Do not incubate in CO₂ except for *Haemophilus*, *N.gonorrhoeae*, Streptococci)

Reading plates and interpreting results:

Examine the plates after 16 - 18 hours of incubation

In case of testing of Staphylococcus for oxacillin and Enterococcus for vancomycin, incubate the plates for 24 hours before reading (other disks on the same plate may be read at 16 -18 hours and the plate re-incubated).

Check for confluence of the growth:

There should be a confluent lawn of growth and zones of inhibition should be uniformly circular if the plate was satisfactorily streaked

If individual colonies are seen, the inoculum was too light and the test should be repeated

Measure the diameters of the zones of inhibition (to the nearest whole number) as observed with the naked eye using a ruler held at the back of the Petri dish.

If the media is opaque (as in the case of blood agar), measure the media from the surface of the agar illuminated with reflected light.

The zone margins are taken as the areas showing no obvious growth as seen with a naked eye. Faint growth of tiny colonies seen only with the aid of a hand lens at the edge of the zone of inhibited growth should be ignored

If discrete colonies are seen within the clear zone of inhibition, repeat the test with a single colony from the primary culture or a purity plate. If the growth of discrete colonies within the zone of inhibition continues upon repeating the test, measure the colony free inner zone.

In case of *Proteus*, a thin veil of swarming growth may be seen within an otherwise clear zone of inhibition. Ignore the swarming and measure the zone of inhibition.

On plates supplemented with blood agar, measure the zones of inhibition and NOT zones of haemolysis

For sulfonamides/trimethoprim (e.g. cotrimoxazole), antagonists in the medium may allow some light growth within the zone of inhibition. Ignore the light growth and measure the more obvious zone.

In testing susceptibility of *Staphylococcus spp* for oxacillin and *Enterococcus spp* for vancomycin, examine the plate with transmitted light for any growth within the zone of inhibition. Any discernable growth within the zone of inhibition is indicative of methicillin or vancomycin resistance respectively.

Record the zone diameters in a table on the work sheet and use the relevant interpretative tables for each organism to record whether the organism is susceptible, intermediate or resistant.

Antibiotic list and Interpretative diameters for *Enterobacteriaceae* (other than *Salmonella/Shigella*)

Media: Muller-Hinton agar

		Zone diameter (mm)			Setting and Reporting guidelines	Special considerations
	Antibiotic	R	I	S		

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	Ampicillin 10µg	≤ 13	14-16	≥ 17	Always set Always report	
	Cefazolin 30µg or Cephalothin 30µg (1 st generation)	≤ 14	15 - 17	≥ 18	Always set Always report	Do not test for CSF isolates. Instead use Ceftriaxone
	Cefuroxime axetil (30µg)	≤ 14	15 - 22	≥ 23	Always set	If resistant test for ESBL

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	(2 nd generation)				Always report	Do not test for CSF isolates. Instead use Ceftriaxone
	Amoxicillin-clavulanic acid (Augmentin) (20/10µg)	≤ 13	14 -17	≥ 18	Always set Always report	If resistant screen for inducible AmpC (If present recommend combination of cephalosporin and aminoglycoside)
	Gentamicin (10µg)	≤ 12	13 - 14	≥ 15	Always set Always report	

	Cotrimoxazole (Trimethoprim- sulfamethoxazole) (1.25/23.5µg)	≤ 10	11 - 15	≥ 16	Always set Always report	Ignore any light growth that may be seen within the clear zone of inhibition (measure the outer zone)
	Chloramphenicol (5µg)	≤ 12	13 - 17	≥ 18	Always set Always report	

	Ciprofloxacin (5µg)	≤ 15	16 - 20	≥ 21	Always set Always report	
	Ceftriaxone (30µg)	≤ 13	14 - 20	≥ 21	Always set Report if requested/if other agents are resistant	Set ESBL confirmatory test for zones of <i>Klebsiella spp</i> , <i>E.coli</i> and <i>Proteus mirabilis</i> that are ≤ 25mm

10.	Ceftazidime 30µg)	≤ 13	14 - 20	≥ 21	Always set Report if requested/if other agents are resistant	Set ESBL confirmatory test for zone of <i>Klebsiella spp</i> , <i>E.coli</i> and <i>Proteus mirabilis</i> that are ≤ 22mm
		Zone diameter (mm)			Setting and Reporting guidelines	Special considerations
	Antibiotic	R	I	S		

11.	Cefotaxime (30µg)	≤ 14	15 - 22	≥ 23	Set as an alternative to Ceftriaxone. Always set for <i>Proteus spp</i>	Set ESBL confirmatory test for zone of <i>Klebsiella spp, E.coli</i> and <i>Proteus mirabilis</i> that are ≤ 27mm
12.	Imipenem(10µg)/ Meropenem (10µg)	≤ 13	14 - 15	≥ 16	Set in case of resistance to Ceftriaxone or demonstration of ESBL	
13.	Nalidixic acid (30µg)	≤ 13	14 - 18	≥ 19	Always set and report for urine isolates only	

14.	Nitrofurantoin 300 µg	≤ 13	15 - 16	≥17	Always set for urine isolates Always report for urine isolates	
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For Salmonella and Shigella:

Faecal isolates:

Set Ampicillin, ciprofloxacin, nalidixic acid, cotrimoxazole (Report all routinely)

Extra-intestinal isolates of *Salmonella spp*: Add chloramphenicol and Ceftriaxone. Exclude nalidixic acid.

Antibiotic list and Interpretative diameters for *Vibrio cholerae*

Media: Muller-Hinton agar

QC strain: ATCC 25922

		Zone diameter (mm)			Setting and Reporting guidelines	Special considerations
	Antibiotic	R	I	S		
	Ampicillin 10µg	≤ 13	14-16	≥ 17	Always set	

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					Always report	
	Trimethoprim-sulfamethoxazole (1.25/23.5µg)	≤ 10	11 - 15	≥ 16	Always set Always report	Ignore the light growth that may be seen within the clear zone of inhibition (measure the outer zone)
	Sulfixazole (250µg)	≤ 12	13 - 16	≥ 17	Always set Always report	

	Tetracycline (30µg)	≤ 14	15 - 18	≥ 19	Always set Always report	
	Chloramphenicol (5µg)	≤ 12	13 - 17	≥ 18	Always set Always report	Test sometimes miss classifies some strains

Disc diffusion should not be conducted for erythromycin as it correlates poorly with MIC results.

Antibiotic list and Interpretative diameters for *Pseudomonas aeruginosa*

Media: Muller-Hinton agar

		Zone diameter (mm)			Setting and Reporting guidelines	Special considerations
	Antibiotic	R	I	S		
1.	Piperacillin 100µg	≤ 17	-	≥ 18	Always set	

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					Always report	
2.	Piperacillin-tazobactam (100µg/10µg)	≤ 17	-	≥ 18	Always set Always report	
3.	Ceftazidime(30µg)	≤ 14	15 - 17	≥ 18	Always set Always report	Heavy inoculum gives erroneous resistance

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4.	Cefepime(30µg)	≤ 14	15 - 17	≥ 18	Set when Ceftazidime is resistant	Heavy inoculum gives erroneous resistance
5.	Gentamicin (10µg)	≤ 12	13 - 14	≥ 15	Always set Always report	
7.	Ciprofloxacin (5µg)	≤ 15	16 - 20	≥ 21	Always set Always report	

8.	Tetracycline(30µg)	≤ 14	15 - 18	≥ 19	Always set Always report	
9.	Imipenem(10µg)/	≤ 13	14 - 15	≥ 16	Set in case of resistance to Ceftazidime or demonstration of ESBL or AmpC	
10.	Amikacin(30µg)	≤ 14	15 - 16	≥ 17	Always set Report in case of resistance to gentamicin. In report, mention that	

					tobramycin and netilimicin are alternatives	
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Antibiotic list and Interpretative diameters for *Acinetobacter spp*

Media: Muller-Hinton agar

		Zone diameter (mm)			Setting and Reporting guidelines	Special considerations
		R	I	S		
	Antibiotic	R	I	S		
1.	Piperacillin 100µg	≤ 17	18 - 20	≥ 21	Always set	

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					Always report	
2.	Piperacillin-tazobactam (100µg/10µg)	≤ 17	18 - 20	≥ 21	Always set Always report	
3.	Ceftazidime(30µg)	≤ 14	15 - 17	≥ 18	Always set Always report	Heavy inoculum gives erroneous resistance

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4.	Cefepime(30µg)	≤ 14	15 - 17	≥ 18	Sethen Ceftazidime is resistant	Heavy inoculum gives erroneous resistance
5.	Trimethoprim-sulfamethoxazole (1.25/23.5µg)	≤ 10	11 - 15	≥ 16	Always set Always report	
5.	Gentamicin (10µg)	≤ 12	13 - 14	≥ 15	Always set Always report	

8.	Ciprofloxacin (5µg)	≤ 15	16 - 20	≥ 21	Always set Always report	
9.	Tetracycline(30µg)	≤ 14	15 - 18	≥ 19	Always set Always report	Represent Minocycline and Doxycycline but some strains that are I or R to tetracycline may be susceptible to the two drugs

10.	Imipenem(10µg)	≤ 13	14 - 15	≥ 16	Set in case of resistance to Ceftazidime or demonstration of ESBL or AmpC	
11.	Amikacin(30µg)	≤ 14	15 - 16	≥ 17	Always set Report in case of resistance to gentamicin. In report, mention that tobramycin and netilmicin are alternatives	

Antibiotic list and Interpretative diameters for *Burkholderia cepacia*

Media: Muller-Hinton agar

		Zone diameter (mm)			Setting and Reporting guidelines	Special considerations
	Antibiotic	R	I	S		

1.	Ceftazidime(30µg)	≤ 17	18 - 22	≥ 21	Always set Always report	Heavy inoculum gives erroneous resistance
2.	Minocycline (30µg)	≤ 14	15 - 18	≥ 19	Always set Always report	Heavy inoculum gives erroneous resistance
3.	Trimethoprim-sulfamethoxazole (1.25/23.5µg)	≤ 10	11 - 15	≥ 16	Always set Always report	

Antibiotic list and Interpretative diameters for *Stenotrophomonas maltophilia*

Media: Muller-Hinton agar

		Zone diameter (mm)	Setting and Reporting guidelines	Special considerations
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	Antibiotic	R	I	S		
1.	Minocycline (30µg)	≤ 14	15 - 18	≥ 19	Always set Always report	Heavy inoculum gives erroneous resistance
2.	Levofloxacin (5µg)	≤ 13	14 - 16	≥ 17	Always set Always report	

3.	Trimethoprim-sulfamethoxazole (1.25/23.5µg)	≤ 10	11 - 15	≥ 16	Always set Always report	
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Antibiotic list and Interpretative diameters for *Staphylococcus spp***Media:** Muller-Hinton agar

	Antibiotic	Zone diameter (mm)			Setting and Reporting guidelines	Special considerations
		R	I	S		
1.	Penicillin G (10 units)	≤ 28	-	≥ 29	Always set Always report	If oxacillin is resistant, always report as resistant
2.	Cefoxitin (30 µg)	≤ 19	-	≥ 20	Always set	Used as a screen for oxacillin resistance. Report as oxacillin resistant or sensitive

		≤ 24 (for CoNS)		≥ 25 (for CoNS)	Always report (as oxacillin resistant or sensitive)	Incubate a full 24 hours
3.	Erythromycin (15µg)	≤ 13	14 - 22	≥ 23	Always set Always report (Do not report for urinary tract)	
4.	Clindamycin (2µg)	≤ 14	15 -20	≥ 21	Always set Report if erythromycin is resistant	Place next to erythromycin disc to text for inducible resistance (erm) (Appendix I)
5.	Vancomycin	-	-	≥ 15	Always set Report if other agents are resistant	Resistant isolates may not be detectable by disc diffusion. For isolates with zone diameters ≤14mm should do MICs

6.	Tetracycline	≤ 14	15 - 18	≥ 19	Always set Always report (except for paediatrics)	
6.	Trimethoprim-sulfamethoxazole (1.25/23.5 μ g)	≤ 10	11 - 15	≥ 16	Always set Always report	Ignore the light growth that may be seen within the clear zone of inhibition (measure the outer zone)
7.	Chloramphenicol (5 μ g)	≤ 12	13 - 17	≥ 18	Always set Always report	
8.	Ciprofloxacin (5 μ g)	≤ 15	16 - 20	≥ 21	Always set Report if requested/if other agents are resistant	Indicate warning that <i>Staphylococcus spp</i> may develop resistance to quinolones during the course of treatment

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9.	Gentamicin (10µg)	≤ 12	13 - 14	≥ 15	Always set Report if requested/if other agents are resistant	
10.	Nitrofurantoin (300µg)	≤ 14	15 - 16	≥ 17	Always set for urine only	
11.	Rifampicin (5µg)	≤ 16	17 - 19	≥ 20	Set in case of oxacillin resistance	Always used in combination with another agent in case of treatment
12.	Linezolid (30µg)	-	-	≥ 20	Set in case of oxacillin resistance	

Antibiotic list and Interpretative diameters for *Enterococcus spp***Media used:** Muller-Hinton Agar **QC strain:** *S. aureus* ATCC 25923. For HLAR test with Gentamicin use *E. faecalis* 29212

	Antibiotic	Zone diameter (mm)			Setting and Reporting guidelines	Special considerations
		R	I	S		
1.	Ampicillin 10µg	≤ 16	-	≥ 17	Always set Always report	Always test blood & CSF isolates for β-lactamase using nitrocefin test. A positive test indicates resistance
2.	Vancomycin 30µg	≤ 14	15 - 17	≥ 18	Always set Report if ampicillin resistant	Always incubate for a full 24 hours. Examine plate with transmitted light. Any haze or any growth within zone of inhibition indicates resistance

		Zone diameter (mm)			Setting and	Special considerations
					Reporting guidelines	
3.	Erythromycin 10µg	≤ 13	14- 22	≥ 23	Always set Report if ampicillin and vancomycin are resistant Do not report for urine isolates	
4.	Tetracycline 30µg	≤ 14	15 -18	≥ 19	Always set Report if resistant to ampicillin and vancomycin	
5.	Gentamicin (120µg)	≤ 6	7 - 9	≥ 10	Always set	A screen for high-level resistance to aminoglycosides. Resistance precludes synergy with β-lactams/vancomycin

		Zone diameter (mm)			Setting and	Special considerations
					Reporting guidelines	
	(HLAR test)				Always report	
6.	Chloramphenicol (30µg)	≤ 12	13 - 17	≥ 18	Always set Report if resistant to vancomycin	
7.	Ciprofloxacin (5µg)	≤ 15	16 - 20	≥ 21	Set for urine isolates only Report if ampicillin resistant	
8.	Nitrofurantoin (300µg)	≤ 14	15 - 16	≥ 17	Set and report for urine only	
9.	Rifampicin (5µg)	≤ 16	17 - 19	≥ 20	Set in case of vancomycin resistance	

		Zone diameter (mm)			Setting and	Special considerations
					Reporting guidelines	
					Report if resistant to vancomycin	
10.	Linezolid (30µg)	≤ 20	21 - 22	≥ 23	Set in case of vancomycin resistance Report if resistant to vancomycin	

Do not test Cephalosporins, clindamycin, cotrimoxazole (SXT) and aminoglycosides (Except HLAR) because they may appear active in vitro but are ineffective clinically

Antibiotic list and Interpretative diameters for *Haemophilus spp*

Media used: Haemophilus test agar

QC strain: *H. influenzae* ATCC 49247, *H. influenzae* ATCC 49766, *E.coli* ATCC 35218 (For Augmentin testing)

		Zone diameter (mm)			Setting and Reporting guidelines	Special considerations
	Antibiotic	R	I	S		

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1.	Ampicillin 10µg	≤ 16	-	≥ 17	Always set Always report (base initial report on nitrocefin disc)	Do Nitrocefin β-lactamase test as initial screen for ampicillin susceptibility
2.	Augmentin (20/10µg)	≤ 19	-	≥ 20	Always set Report if ampicillin resistant Do not report for CSF	Used empirically in treating respiratory tract infections. Susceptibility testing mainly for surveillance purposes

3.	Tetracycline 30µg	≤ 25	26 -28	≥ 29	Always set Report only for ampicillin resistant isolates Do not report for CSF/children	
6.	Chloramphenicol (30µg)	≤ 25	26 -28	≥ 29	Always set Report if ampicillin resistant	

7.	Trimethoprim- sulfamethoxazole (1.25/23.5µg)	≤ 10	11 - 15	≥ 16	Always set Always report Do not report for CSF	
8.	Ciprofloxacin (5µg)	-	-	≥ 21	Always set Report if ampicillin resistant Do not report for CSF	

9.	Cefuroxime (30µg) (For both oral and parenteral preparations)	≤ 16	17 - 19	≥ 20	Always set Do not report Do not report for CSF	Used empirically in treating respiratory tract infections. Susceptibility testing mainly for surveillance purposes
10.	Ceftriaxone	-	-	≥ 26	Always set Report only for CSF and blood	In case of diameters ≤26 set MICs

11.	Rifampicin (5µg)	≤ 16	17 - 19	≥ 20	Set in case of all other drugs are resistant Report if resistant to other drugs	
12.	Meropenem	-	-	≥ 20	Set in case of all other drugs are resistant Report if resistant to other drugs	

For Ceftriaxone, ciprofloxacin and meropenem, resistance has not been defined. If zones smaller than the susceptible category are seen, reconfirm identification and susceptibility then keep isolate for further study.

Antibiotic list and Interpretative diameters for *Neisseria gonorrhoeae***Media used:** GC agar base (with 1% defined supplement)**Incubation:** 35-37°C in CO₂Susceptibility testing for *N. gonorrhoeae* is only for research and epidemiological purposes.

		Zone diameter (mm)			Setting and	Special considerations
		R	I	S	Reporting guidelines	
	Antibiotic					
1.	Penicillin G 10 units	≤ 26	27 - 46	≥ 47	Always set	nitrocefin β-lactamase test should be conducted.

					Always report	
2.	Ceftriaxone (30µg)	-	-	≥ 34	Always set Always report	In case zone <34mm, confirm the identification and the susceptibility result. Save the isolate for confirmation by a reference lab.
3	Cefuroxime (30µg) (parenteral)	≤ 25	26 - 30	≥ 31	Always set Report upon request	
3.	Cefoxitin (30µg)	≤ 23	24 -27	≥ 28	Always set Report upon request	
6.	Cefpodoxime (30µg)	-	-	≥ 29	Always set Report upon request	In case zone <29mm, confirm the identification and the susceptibility result. Save the isolate for confirmation by a reference lab.

7.	Tetracycline (30µg)	≤ 30	31 - 37	≥ 38	Always set Report upon request	
8.	Ciprofloxacin (5µg)	≤ 27	28 - 40	≥ 41	Always set Always report	
9.	Spectinomycin (100µg)	≤ 14	15 - 17	≥ 18	Always set Report upon request	

Antibiotic list and Interpretative diameters for *Streptococcus pneumoniae***Media used:** Muller-Hinton agar with 5% sheep blood**Incubation:** 35-37°C in CO₂ for 20 - 24 hours

	Antibiotic	Zone diameter (mm)			Setting and Reporting guidelines	Special considerations
		R	I	S		
1.	Oxacillin (1µg)	-	-	≥ 20	Always set Always report (as penicillin and cephalosporin susceptibility)	All isolates with zone diameters ≥ 20mm are reported as susceptible to all penicillins and Cephalosporins. If zone diameters are < 19mm, set MICs for penicillin, and Ceftriaxone

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2.	Erythromycin (15µg)	≤15	16 - 20	≥ 20	Always set Always report (Except for CSF)	
3.	Clindamycin (2µg)	≤ 15	16 - 18	≥ 19	Always set Report if other antibiotics are resistant Do not report for CSF & UTI	
4.	Trimethoprim-sulfamethoxazole (1.25/23.5µg)	≤ 15	16 - 18	≥ 19	Always set Always report (except for CSF)	
5.	Chloramphenicol (30µg)	≤ 20	-	≥ 21	Always set	

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					Always report (Except for urine)	
6.	Tetracycline (30µg)	≤ 18	19 - 22	≥ 23	Always set Always report (Except for children and CSF)	
7.	Sparfloxacin (5µg)	≤ 15	16 - 18	≥19	Always set Report if other antibiotics are resistant Do not report for CSF	

Antibiotic list and Interpretative diameters for *Streptococcus spp* other than *S. pneumoniae*

Media used: Muller-Hinton agar with 5% sheep blood

Incubation: 35-37°C in CO₂ for 20 - 24 hours

In this protocol the term β -haemolytic Streptococci refers to large colony forming strains (i.e. *S.pyogenes*, *S. agalactiae* and group C and G strains with large colonies)

The term viridans Streptococci refers to the viridans group but also includes small colony forming β -haemolytic Streptococci

Testing should not be conducted routinely for *S. pyogenes* and *S. agalactiae* as these are known to be susceptible to penicillin, other β -lactams and vancomycin. Testing is only for research purposes. Any strain found not to be susceptible to these antibiotics should be re-identified and retested

Freeze isolates of *S.pyogenes* for subsequent study

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	Antibiotic	Zone diameter (mm)			Setting and Reporting guidelines	Special considerations
		R	I	S		
1.	Penicillin G(10IU)	-	-	≥ 24	Set only for research purposes Do not set for viridans Streptococci	Test has been standardised only for β-haemolytic Streptococci (<i>S.pyogenes</i> , <i>S. agalactiae</i> and group C & G with large colonies)
2.	Ceftriaxone 30 µg (for β-haemolytic Streptococci)	-	-	≥ 24	In case of <i>S.pyogenes</i> and <i>S. agalactiae</i> set only for research	Zones diameters differ between β-haemolytic Streptococci and viridans Streptococci

	(for viridans Streptococci)	<24	25 -26	≥ 27	Always Report for the viridans group	
3.	Erythromycin (15µg)	≤15	16 - 20	≥ 20	Set for viridans or allergic patients Always report when set	Result is particularly important in patients with allergy to penicillin
4.	Clindamycin (2µg)	≤ 15	16 - 18	≥ 19	Set for viridans Report if other antibiotics are resistant	Place next to erythromycin disc to test for inducible resistance (erm) (appendix I)
5.	Chloramphenicol (30µg)	≤ 17	18 - 20	≥ 21	Always set for viridans Report in case resistant to β-lactams	
6.	Vancomycin (30µg)	-	-	≥17	Set for viridans	

					Report if other antibiotics are resistant	
7.	Tetracycline (30µg)	≤ 18	19 - 22	≥ 23	Always set for viridans Report in case resistant to β-lactams Do not report in children)	

Quality control

Control tests will be conducted on a schedule summarised in Table 7.1

Schedule for quality controls for the Kirby-Bauer antimicrobial susceptibility testing

Reason for QC	Frequency	Comments
Routine	Once weekly	At beginning of this protocol QC shall be conducted daily until 20 consecutive days of satisfactory results are achieved.
When a new batch of susceptibility testing media is prepared	Once for each batch	

When a new lot number or shipment of discs is used	Once for each lot number/shipment	
When any change in the SOP is implemented	Test daily until satisfactory results are obtained on 20 consecutive days	

Antibiotics and Q.C strains to test for Muller-Hinton agar without Blood and the acceptable limits of zone diameters(in mm)

Antimicrobial agent	<i>E.coli</i> (ATCC25922)	<i>S. aureus</i> (ATCC25923)	<i>Pseudomonas aeruginosa</i> (ATCC27853)	<i>E.coli</i> (ATCC35218) For testing β -lactamase inhibitors	<i>Klebsiella pneumoniae</i> (ATCC 700603) For ESBL
Amikacin (30 μ g)	19 - 26	20 - 26	18 - 26	Not tested	Not tested
Ampicillin (10 μ g)	16 - 22	27 - 35	Not tested	6	Not tested

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Augmentin(20/10µg)	18 - 24	28 - 36	Not tested	17 - 22	Not tested
Cefotaxime (30µg)	29 - 35	25 - 31	18 - 22	Not tested	17 - 25
Ceftriaxone (30µg)	29 - 35	22 - 28	17 - 23	Not tested	16 - 24
Ceftazidime (30µg)	25 - 32	16 - 20	22 - 29	Not tested	10 - 18
Cefuroxime (30µg)	20 - 26	27 - 35	Not tested	Not tested	Not tested

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Cephalothin (30µg)	15 - 21	29 - 37	Not tested	Not tested	Not tested
Chloramphenicol (30µg)	21 - 27	19 - 26	Not tested	Not tested	Not tested
Ciprofloxacin (5µg)	30 - 40	22 - 30	25 - 33	Not tested	Not tested
Erythromycin (15µg)	Not tested	22 - 30	Not tested	Not tested	Not tested
Gentamicin (10µg)	19 - 26	19 - 27	16 - 21	Not tested	Not tested

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Imipenem (10µg)	26 - 32	Not tested	20 - 28	Not tested	Not tested
<i>Linezolid (30µg)</i>	<i>Not tested</i>	25 - 32	<i>Not tested</i>	<i>Not tested</i>	Not tested
Meropenem (10µg)	28 - 34	29 - 37	27 - 33	Not tested	Not tested
Nalidixic acid (30µg)	22 - 28	Not tested	Not tested	Not tested	Not tested
Nitrofurantoin (300µg)	20 - 25	18 - 22	Not tested	Not tested	Not tested

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Oxacillin (1µg)	Not tested	18 - 24	Not tested	Not tested	Not tested
Penicillin (10units)	-	26 - 37	Not tested	Not tested	Not tested
Piperacillin (100µg)	24 - 30	Not tested	25 - 33	Not tested	Not tested
Rifampicin (5µg)	8 - 10	26 - 34	Not tested	Not tested	Not tested
Sparfloxacin (5µg)	30 - 38	27 - 33	21 - 29	Not tested	Not tested

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Sulfisoxazole (250 or 300µg)	15 - 23	24 - 34	Not tested	Not tested	Not tested
Tetracycline (30µg)	18 - 25	24 - 30	Not tested	Not tested	Not tested
Trimethoprim-Sulfamethoxazole (1.25/23.75µg)	23 - 29	24 - 32	Not tested	Not tested	Not tested
Vancomycin (30µg)	Not tested	17 - 21	Not tested	Not tested	Not tested

Highlighted antimicrobial agents need not be tested routinely

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Antibiotics and Q.C strains to test for fastidious organisms and the acceptable limits of zone diameters(in mm)

Antimicrobial agent	<i>H.influenzae</i> (ATCC49247) Haemophilus medium test	<i>H.influenzae</i> (ATCC49766) Haemophilus medium test	<i>Neisseria gonorrhoeae</i> (ATCC49226) Supplemented G.C agar	<i>Streptococcus pneumoniae</i> (ATCC49619) Muller-Hinton agar supplemented with 5% sheep blood
Ampicillin (10µg)	13 - 21	Not tested	Not tested	30 - 36

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Augmentin(20/10µg)	15 - 23	Not tested	Not tested	Not tested
Ceftriaxone (30µg)	31 - 39	Not tested	39 - 51	30 -35
Cefuroxime (30µg)	Not tested	28 - 36	33 - 41	Not tested
Chloramphenicol (30µg)	31 - 40	Not tested	Not tested	23 - 27
Ciprofloxacin (5µg)	34 - 42	Not tested	48 - 58	Not tested

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Erythromycin (15µg)	Not tested	Not tested	Not tested	25 - 30
<i>Linezolid (30µg)</i>	<i>Not tested</i>	25 - 32	<i>Not tested</i>	25 - 34
Meropenem (10µg)	20 - 28	Not tested	Not tested	28 - 35
Oxacillin (1µg)	Not tested	Not tested	Not tested	< 12
Penicillin (10units)	Not tested	Not tested	26 - 34	24 - 3

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Rifampicin (5µg)	22 - 30	Not tested	Not tested	25 - 30
Sparfloxacin (5µg)	32 - 40	Not tested	43 - 51	21 - 27
Tetracycline (30µg)	14 - 22	Not tested	30 - 42	27 - 31
Trimethoprim- Sulfamethoxazole (1.25/23.75µg)	24 - 32	Not tested	Not tested	20 - 28

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Vancomycin (30µg)	Not tested	Not tested	Not tested	20 - 27
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Disc diffusion Q.C trouble shooting when using Muller-Hinton agar

Repeat out of range tests

If issue is unresolved after repeating, troubleshoot using the table below

Inform suppliers of any suspected manufacturing problem

QC organisms should be well maintained: Avoid repeated subcultures. Retrieve new Q.C strains from stock. Maintain the Q.C strains at -80°C and prepare working stock cultures weekly. Avoid repeated subcultures

Antimicrobial agent	QC strain	Observation	Probable cause	Comments/Action
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Aminoglycosides	Any	Zone too small	pH of media too low	Acceptable pH range is 7.2 - 7.4 Avoid incubation in CO ₂ (it lowers pH)
Aminoglycosides	Any	Zone too large	pH of media too high	Acceptable pH range is 7.2 - 7.4 (check media pH)

Aminoglycosides	<i>Pseudomonas aeruginosa</i> (ATCC 27853)	Zone too small	Ca ²⁺ or Mg ²⁺ content too high	Use alternative lot of media
Aminoglycosides	<i>Pseudomonas aeruginosa</i> (ATCC 27853)	Zone too large	Ca ²⁺ or Mg ²⁺ content too low	Use alternative lot of media
Augmentin	<i>E.coli</i> ATCC 35218	Zone too small	Disc has lost potency (clavulanic acid is labile)	Use alternative lot of disc check storage conditions and package integrity

Ampicillin	<i>E.coli</i> ATCC 35218	Zone too large (should be no zone-resistant)	Spontaneous loss of the β -lactamase plasmid	Store organisms as mentioned above and avoid repeated subcultures
β -lactams	Any	Zone initially acceptable but decreases and goes out of range over time	Disc has lost potency	Use alternative lot of disc check storage conditions and package integrity Imipenem and clavulanic acid are particularly labile

Antimicrobial agent	QC strain	Observation	Probable cause	Comments/Action
Azetroenam, Cefotaxime, Cefpodoxime, Ceftazidime, Ceftriaxone	<i>Klebsiella pneumoniae</i> (ATCC700603)	Zone too large	Spontaneous loss of the β -lactamase plasmid	Store organisms as mentioned above and avoid repeated subcultures
ESBL confirmatory test	<i>Klebsiella pneumoniae</i> (ATCC700603)	Negative ESBL confirmatory test	Spontaneous loss of the β -lactamase plasmid	Store organisms as mentioned above and avoid repeated subcultures

Penicillin	Any	Zone too large	pH of media too low	Acceptable pH range is 7.2 - 7.4. Avoid incubation in CO ₂ (it lowers pH)
Penicillin	Any	Zone too small	pH of media too high	Acceptable pH range is 7.2 - 7.4 (check media pH)
Clindamycin	<i>S. aureus</i> (ATCC25923)	Zone too small	pH of media too low	Acceptable pH range is 7.2 - 7.4. Avoid

				incubation in CO ₂ (it lowers pH)
Clindamycin	<i>S. aureus</i> (ATCC25923)	Zone too large	pH of media too high	Acceptable pH range is 7.2 - 7.4 (check media pH)
Macrolides	<i>S. aureus</i> (ATCC25923)	Zone too small	pH of media too low	Acceptable pH range is 7.2 - 7.4. Avoid incubation in CO ₂ (it lowers pH)

Macrolides	<i>S. aureus</i> (ATCC25923)	Zone too large	pH of media too high	Acceptable pH range is 7.2 - 7.4 (check media pH)
Quinolones	Any	Zone too small	pH of media too low	Acceptable pH range is 7.2 - 7.4. Avoid incubation in CO ₂ (it lowers pH)

Antimicrobial agent	QC strain	Observation	Probable cause	Comments/Action
Quinolones	Any	Zone too large	pH of media too high	Acceptable pH range is 7.2 - 7.4 (check media pH)
Tetracyclines	Any	Zone too large	pH of media too low	Acceptable pH range is 7.2 - 7.4. Avoid incubation in CO ₂ (it lowers pH)

Tetracyclines	Any	Zone too small	pH of media too high	Acceptable pH range is 7.2 - 7.4 (check media pH)
Tetracyclines	Any	Zone too small	Ca ²⁺ /Mg ²⁺ too high	Use alternative lot of media
Tetracyclines	Any	Zone too large	Ca ²⁺ /Mg ²⁺ too low	Use alternative lot of media

Sulfonamides, Cotrimoxazole	E.faecalis (ATCC 29212)	Zone \leq 20 mm	Media too high in thymidine content	Use alternative lot of media
Various	Any	Many zones too large	Inoculum too light, error in inoculum preparations, media too thin, MHA nutritionally unacceptable	Repeat inoculum preparation Check expiry date and storage of the barium sulphate turbidity standard Use correct agar depth (about 4mm)

				Recheck with another lot of MHA
Various	Any	Many zones too small	Inoculum too heavy, error in inoculum preparations, media too thick, MHA nutritionally unacceptable	Repeat inoculum preparation Check expiry date and storage of the barium sulphate turbidity standard Use correct agar depth (about 4mm)

				Recheck with another lot of MHA
Antimicrobial agent	QC strain	Observation	Probable cause	Comments/Action
Various	Any	One or more zones too small or too large	Measurement error, transcription error, Random defective disc, disc not pressed firmly against the agar	Check reading for measurement or transcription errors Retest. If retest results are out of range and no error has been detected initiate corrective action

<p>Various</p>	<p><i>S.pneumoniae</i> (ATCC 49619)</p>	<p>Zones too large Lawn of growth scanty</p>	<p>Inoculum source plate is too old with too many non-viable cells Plate used to prepare inoculum should be 18 - 24 hours</p>	<p>Sub-culture QC strain and repeat the test Or retrieve new QC strain</p>
<p>Various</p>	<p>Any</p>	<p>One QC strain is out of range but others are in range with the same antibiotic</p>	<p>One Q.C organism may be a better indicator of the QC problem</p>	<p>Retest the strain for reproducibility of acceptable results</p>

				<p>Evaluate the alternative strains with known MICs</p> <p>Initiate corrective action with the problem QC strain/antimicrobial agents</p>
Various	Any	2 QC strains out of range with the same antimicrobial agent	Indicative of a problem of the disc	<p>Use alternative lot of discs</p> <p>Check storage conditions and Package integrity</p>

Various	Any	Zones overlap	Too many discs per plate	Place no more than 12 discs on 150mm plates and five discs on 100mm plates; for some fastidious bacteria that produce large zones use fewer discs
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Annex 1: SOP ATTESTATION FORM

Attestation Record (general staff SOP Review At least annually)		
{Please ensure that you have read and understood before signing}		
Names	Signature	Date

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