Sodium and potassium disturbances in childhood diarrhoea

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ABSTRACT

BACKGROUND

Diarrhoea is the one of the leading causes of childhood death globally and in South Africa. Plasma sodium and potassium disturbances contribute to this diarrhoea mortality, partly mediated by seasonal fluctuations in the disturbances. The high prevalence and the potentially serious implications of plasma sodium and potassium disturbances raise several issues about their prevention, diagnosis and management.

OBJECTIVES

a) To identify determinants, particularly with seasonal associations, of plasma sodium and potassium concentrations in young children admitted to hospital with dehydrating diarrhoea.

b) To assess the diagnostic accuracy and reliability of clinical features previously reported to be associated with plasma sodium and potassium disturbances in children admitted to a diarrhoea Rehydration Unit.

c) To perform a preliminary assessment of the amount of change in clinical management as a result of routine electrolyte testing in children with dehydrating diarrhoea.

METHODS

Three separate cross-sectional analytical studies - with overlapping data collection - were conducted during 15 April 2002 to 14 April 2003 on patients between 6 weeks and 2 years of age admitted to the Rehydration Unit at Red Cross Children's Hospital, Cape Town.

RESULTS AND INTERPRETATION

Study one: Seasonal determinants of plasma sodium and potassium concentrations

Results: Of the 350 patients included in the study, plasma sodium levels were available for 348 (99.4%) patients and plasma potassium for 347 (99.1%) patients. Determinants with statistically significant negative associations ($p<0.05$) with plasma sodium in multiple linear regression analysis were age (-0.29 mmol/l), plasma pH (-22.13 mmol/l), enterotoxigenic *Escherichia coli* infection (-2.13 mmol/l) and enteropathogenic *Escherichia coli* infection (-5.12 mmol/l). Statistically significant positive associations with plasma sodium in multiple linear regression analysis were being breast-fed (1.91 mmol/l) and living in a brick house (2.66 mmol/l).

Determinants with statistically significant negative associations with plasma potassium in multiple regression linear analysis were duration of diarrhoea (-0.02 mmol/l) before admission and Cryptosporidium infection (-0.33 mmol/l). Statistically significant positive associations ($p<0.05$) with plasma potassium in multiple linear regression analysis were parental education (0.04 mmol/l) and plasma pH (1.68 mmol/l).

Enterotoxigenic *Escherichia coli* and Cryptosporidium infection had significant associations, in the same direction, with both plasma sodium and potassium in the bivariate analysis.

Interpretation: Seasonal fluctuations in plasma sodium and potassium levels are at least partly explained by both enterotoxigenic *Escherichia coli* and Cryptosporidium working together, with enterotoxigenic *Escherichia coli* having the larger effect on plasma sodium levels and Cryptosporidium on plasma potassium levels. The associations of these enteropathogens with the seasonal fluctuations in plasma sodium and potassium levels is a new contribution to the current body of research.

Study two: Reliability and diagnostic accuracy of clinical signs

Results: Of the 476 patients enrolled into the study, 475 (99.8%) were included in the final analysis for plasma sodium and 471 (98.9%) for plasma potassium. One hundred and eighty-seven patients (39.4%) had plasma sodium levels <135 mmol/l and 31 (6.5%) levels >150 mmol/l. Two hundred and thirty-six patients (50.1%) had plasma potassium levels <3.5 mmol/l.

Inter-observer agreement in assessing clinical signs was generally poor. Exceptions were abdominal distension (weighted Kappa 0.70; 95% CI 0.49 to 0.91); ability to sit (weighted Kappa 1.0; 95% CI 1.0 to 1.0); and to stand (weighted Kappa 0.72; 95% CI 0.44 to 0.99). Clinicians had no agreement as to whether there was a wooden feel to the patients' skin (- 0.02; 95% CI – 1.24 to 1.21).

None of the signs studied for diagnostic accuracy had clinically meaningful associations with any of the plasma sodium and potassium abnormalities.

Interpretation: This is the first systematic study of the diagnostic accuracy of clinical signs of plasma sodium and potassium disturbances in children with diarrhoea. The clinical signs assessed were neither useful nor reliable in clinical practice, with a consistent pattern of low accuracy across all tests.

Even though there is uncertainty around the estimates of diagnostic accuracy for less prevalent conditions because of low statistical power, the most optimistic plausible levels of accuracy are not clinically meaningful, given the low prevalence of the target conditions.

Study three: Therapeutic impact of routine electrolyte testing in management of plasma sodium and potassium disturbances

Results: Of the 530 patients included in the analysis, plasma sodium levels were available for 528 (99.6%) patients and plasma potassium for 525 (99.1%) patients. Routine electrolyte testing identified 55 (10.4%) with abnormal plasma sodium levels, 18 (3.4%) of which were below 125 mmol/l, 37 (7.0%) above 150 mmol/l and 23 (4.4%) above 155 mmol/l. One hundred and sixty-six (31.6%) patients had low potassium levels, with 40 (7.6%) below 2 mmol/l and 13 (2.5%) below 1.5 mmol/l.

The number of patients that needed to be tested for each case that received a change in management was high because of the relatively low prevalence of some abnormalities. For potassium levels <1.5 mmol/l, the number needed to test was between 40 and 44 patients for any management change (95% CI ranged from 26 to 99). Even larger numbers (48 patients; 95% CI 30 to 116 patients) needed to be tested for one management change in hyponatraemia (plasma sodium <125 mmol/l). For more prevalent and less severe conditions, for example, hypokalaemia (potassium <3 mmo/l), fewer patients needed testing (3 to 4) to identify one patient and to change management (5 to 7 patients).

Interpretation: This is the first study to report on the therapeutic impact of routine electrolyte testing in a low- or middle-income country. Routine testing resulted in the detection of plasma sodium and potassium abnormalities. However, large numbers of patients needed to be tested for each case of management change when abnormalities had a relatively low prevalence.

The benefits of such testing need to be weighed against the costs of performing many tests before one abnormality is identified and treated, taking into consideration the presence of other health priorities, financial constraints and limited facilities and staffing in most settings were dehydrating diarrhoea is more prevalent.

DECLARATION

I, *Victoria Pillay*, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.
I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: _____

Date: May 2006

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GLOSSARY

Colinearity

A situation where there is close to a near perfect linear relationship among some or all of the independent variables in a regression model. This means there is some degree of redundancy or overlap among these variables.

Co-morbidity

The presence of co-existing or additional diseases with reference to an initial diagnosis or with reference to the index condition that is the subject of study.

Disability-adjusted life years

A quantitative indicator of burden of disease that reflects the total amount of healthy life lost, to all causes, whether from premature mortality or from some degree of disability during a period of time.

Effect modifier

A factor that modifies the effect of the independent variable on the dependent variable.

False-negative

A negative test result for the target condition in a person who is actually positive.

False-positive

A positive test result for the target condition in a person who is actually negative.

Inter-observer variation

Variations between different observers when reporting on the same outcomes at the same time.

Kappa score

A measure of the degree of non-random agreement between observations or measures of the same categorical variable. Kappa is always less than or equal to one. A value of one implies perfect agreement and values less than one imply less than perfect agreement. Kappa can be negative - a sign that the two observers agreed less than would be expected just by chance.

Suggested interpretation of Kappa (Sackett *et al.*, 1991:30):
0 = no agreement better than chance,
0 – 0.2 = slight agreement,
0.2 – 0.4 = fair agreement,
0.4 – 0.6 = moderate agreement,
0.6 – 0.8 = substantial agreement,
0.8 – 1.0 = almost perfect agreement.

Likelihood ratio

The ratio of the likelihood that a given test result is expected in a patient with the target disorder compared to the likelihood that that same result is expected in a patient without the target disorder. It is a measure of how much a given diagnostic test result (positive or negative) will raise or lower the pre-test odds of a disorder.

Number needed to test

The number of patients who need to be tested to identify one additional patient with the target condition.

Outlier

An extreme case in one variable, or a combination of variables, which have a strong influence on the calculation of summary statistics.

Post-test probability

The probability of the target condition being present after the results of the diagnostic test are available.

Predictive value negative

The probability that a person does not have the disease given a negative test.

Predictive value positive

The probability that a person has the disease given a positive test result.

Pre-test probability

The probability of the target condition being present before the results of the diagnostic test are available

Reliability

The extent to which a measure is stable or consistent and produces similar results when administered repeatedly.

Receiver operating characteristic curve

"A figure depicting the power of a diagnostic test. The receiver operating characteristic curve presents the test's true positive rate (sensitivity) on the horizontal axis and the false-positive rate (1-specificity) on the vertical axis for different cut-points dividing a positive from a negative test. A receiver operator curve for a perfect test has an area under the curve = 1.0 while a test that performs no better than by chance has an area under the curve of only 0.5. These curves help select the best combination of sensitivity and specificity with the area under the curve being a summary statistic of overall accuracy" (Guyatt & Rennie, 2002:425).

Selection bias

The introduction of error due to systematic differences in the characteristics of those selected to participate in a study. In *sampling bias*, which is a type of selection bias, error results from failure to ensure that all members of the reference population have a known chance of being selected for inclusion in the sample. In allocation bias, error results from systematic differences in the characteristics of those assigned to treatment versus control groups in a

controlled study. Allowing potential participants to self-select for participation or for intervention introduces selection bias.

Sensitivity

The proportion of truly diseased persons in a screened population who are identified as being diseased by the test. It is a measure of the probability of correctly diagnosing a condition.

Specificity

The proportion of truly non-diseased persons who are so identified by the screening test. It is a measure of the probability of correctly identifying a non-diseased person.

Spectrum bias

Patients with only particular demographics, co-morbidities and severity of the target condition are included in the study sample, resulting in variability in the measure of test accuracy.

Test review bias

The distortion of the measures of accuracy caused by knowledge of the result of the reference standard while interpreting the index test.

Variance inflation factor

The impact of colinearity among the independent variables in a regression model on the precision of estimation. It expresses the degree to which colinearity among the independent variables degrades the precision of an estimate.

Verification bias

This occurs when a study selectively includes patients based on positive or negative results of preliminary testing, or the study test itself. To avoid this, a study should include consecutive patients at risk for a particular disease, and not only a subset who underwent definitive testing.

Weighted Kappa

When more than two categories are ordered, weighted Kappa takes account of the degree of disagreement by giving weights to disagreements according to the size of the discrepancy in agreement. Weighted Kappa is usually higher than unweighted Kappa for the same observers and observations.

ABBREVIATIONS

β	Beta
DALYs	Disability-adjusted life years
EAEC	Enteroaggregative *Escherichia coli*
EPEC	Enteropathogenic *Escherichia coli*
ETEC	Enterotoxigenic *Escherichia coli*
KCl	Potassium chloride
LR	Likelihood ratio
mmol/l	Milli mole per litre
NNT	Number needed to test
SADHS	South African Demographic Household Survey
UNICEF	United Nations Children's Fund
VIF	Variance inflation factor

CHAPTER ONE: INTRODUCTION

1.1 The magnitude of the problem of diarrhoeal disease

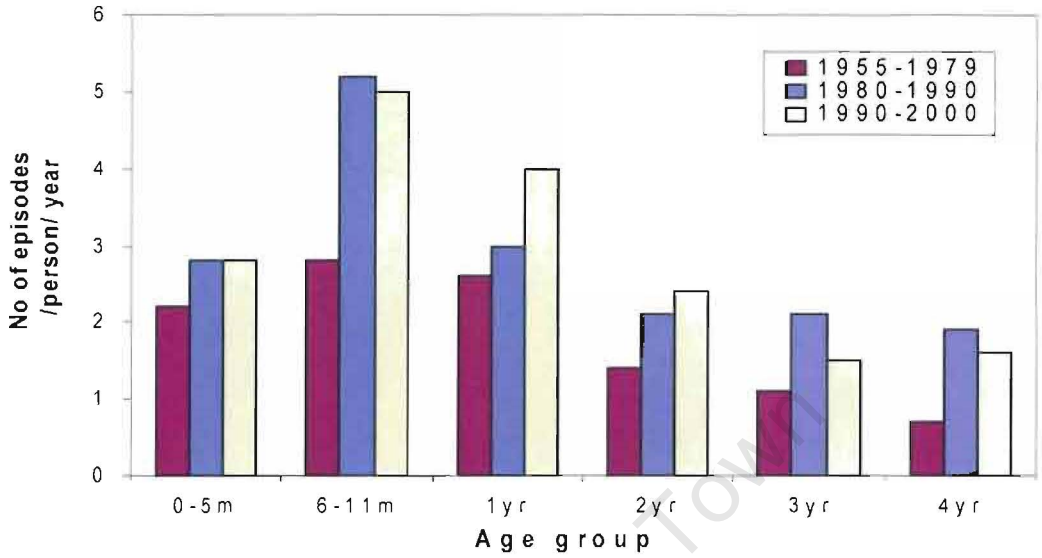
1.1.1 Globally

In 1990 an estimated 98% of all deaths globally in children younger than 15 years of age occurred in developing countries. Thirty-two percent of these deaths were in children under 5 years of age (Murray & Lopez, 1997a). One of the major contributors to this childhood mortality is diarrhoeal disease, despite progress in the understanding of the pathogenesis and management of the disease (Thapar & Sanderson, 2004).

Between 1992 and 2000 in the developing world, 4.9 children per 1000 per year died as a result of diarrhoea in the first five years of life. Even though there has been a decline in mortality rates over the years, from 13.6 (between 1955 and 1979) to 5.6 (between 1980 and 1989) per 1000 per year, morbidity rates were observed to be greater than in earlier years (Kosek *et al.*, 2003).

The overall burden of disease due to diarrhoea is massive, with an estimated loss of 99.6 million disability-adjusted life years (DALYs) annually worldwide (Murray & Lopez, 1997b). The median diarrhoea incidence for all children under 5 years was 3.2 episodes per child per year (Figure 1.1) (Kosek *et al.*, 2003).

Figure 1.1 Median age-specific incidences for diarrhoeal episodes per child per year from three reviews of prospective studies in developing areas, 1955-2000 (Kosek *et al.*, 2003).



1.1.2 In South Africa

Mortality data for South Africa are unreliable because of under-registration and misclassification (Bradshaw *et al.*, 2003a), and morbidity data are limited (Bradshaw, D. 2004. Personal Communication. 14 May, Medical Research Council, Cape Town). Diarrhoea is still, however, reported as one of the top three leading causes of childhood death. It was reported to account for 10.2% of the 106 070 deaths of specified cause in children aged under 5 years in 2000 (Bradshaw *et al.*, 2003b).

1.1.3 In the study setting

The South African Demographic Household Survey (SADHS) performed in 1998 reported a 13% prevalence of diarrhoea for children under the age of 5 years in the Western Cape (Department of Health. SADHS, 1998). Estimates were derived from the number of children who had diarrhoea in the 2 weeks prior to the survey. Interestingly, the increase in morbidity reported in the global burden of disease study (Kosek *et al.*, 2003) was also observed for the City of Cape Town, with an 8% increase in the number of children under 5

years with diarrhoea between 2000 (83.3 per 1000) and 2001 (91.8 per 1000) (Health Systems Trust, 2003).

The Red Cross Children's Hospital, located in Cape Town South Africa, serves large parts of metropolitan Cape Town. According to routine hospital data for 2001 to 2003, 20% of non-surgical admissions annually are due to diarrhoea (Swingler, G. 2005. Personal Communication. 15 June, Institute of Child Health, Cape Town).

1.2 Factors associated with diarrhoea

1.2.1 Globally

Diarrhoea is endemic to regions with poor socio-economic conditions. These conditions include poor nutritional status, lack of access to safe water and poor sanitation. These factors contribute to the burden of diarrhoeal disease. According to United Nations Children's Fund (UNICEF), one-quarter of people globally in the developing world are still malnourished, 1.1 billion do not have access to safe drinking water and 2.4 billion are without adequate sanitation (UNICEF, 2002).

1.2.2 Socio-economic profile of South Africa

South Africa is a country with a high prevalence of many conditions associated with diarrhoea. The country has a relatively youthful population, with a third of the population being under the age of 15 years (Bradshaw *et al.*, 2003b; Department of Health. SADHS, 1998). Overall, the social conditions in South Africa are poor. About 7% of the women of childbearing age (15-49 years) have received no education. Only 38.9% have piped water inside their house and 46% have their own flush toilet. Half (51%) of the population have homes with plaster as the main wall finish and 12% have bare brick or cement blocks. The rest of the population live in houses made of plastic/cardboard (3.0%), mud (14.3%), mud and cement (8.9%),

corrugated iron/zinc (8.0%) and prefabricated materials (0.4%). These housing characteristics reflect poor socio-economic status and increased environmental exposure (Department of Health. SADHS, 1998).

1.2.3 Socio-economic profile of the study setting

Even though the Western Cape is one of the more affluent provinces in the country, 4% of the households still don't have piped water inside their houses and 2% of the women of childbearing age have no education. Cape Town is situated in the Western Cape Province, the Cape Town metropolis, accounting for approximately 70% of the province's population (Provincial Administration of the Western Cape, 1995).

1.3 Electrolyte disturbances in childhood diarrhoea

1.3.1 Why electrolyte disturbances are important

After dehydration and malnutrition, electrolyte disturbances are an important contributor to morbidity and mortality in children with diarrhoea internationally (Islam & Khan, 1986; Puffer & Serrano, 1973; Purohit & Jyotsna, 1971; Raghu *et al.*, 1981).

Many electrolytes are essential in maintaining the normal functioning of the body, with plasma sodium and potassium being two of vital importance. Normal limits for plasma sodium are 135 - 150 mmol/l and for plasma potassium 3.5 - 5.3 mmol/l. If water or electrolyte levels rise or fall beyond normal limits many bodily functions fail to proceed at their normal rates.

Plasma sodium, a predominant cation (positively charged ion) of extracellular fluid, is crucial in regulating fluid balance in the body. It also plays a vital role in the excitability of muscles and neurones. Plasma sodium levels are closely regulated by kidney function (Gibbs *et al.*, 2002:1724). Both abnormally low plasma sodium levels (hyponatraemia; plasma sodium below 135 mmol/l)

and abnormally high plasma sodium levels (hypernatraemia; plasma sodium above 150 mmol/l) are associated with severe complications of the central nervous system, namely cerebral oedema in hyponatraemia and shrinkage of the brain in hypernatraemia, ultimately resulting in neurological dysfunction and/or death, especially when hypernatraemia is above 158 mmol/l (Adelman & Solhung, 1996:218; Bruck *et al.*, 1968; Caksen *et al.*, 2001; Finberg, 1986, Islam & Khan, 1986; Paneth, 1980). Other conditions associated with hypernatraemia are severe acidosis and respiratory failure (Haddow & Cohen, 1974; John Hopkins, 2002:244).

Potassium is the major cation (positively charged ion) of intracellular fluid. As with plasma sodium, it is extremely important in the correct functioning of excitable cells such as muscles, neurones and sensory receptors. It is also vitally important in the regulation of fluid levels within the cell and in maintaining the correct pH balance within the body (Gibbs *et al.*, 2002:1727). Hypokalaemia (potassium levels <3.5 mmol/l) can result in a range of severe disorders, for example, a paralytic ileus, muscle weakness, respiratory paralysis and arrhythmias leading to cardiac arrest (Mrozowski, 1996:322; Rudzinski *et al.*, 1996:346). Very low potassium levels (<2.5 mmol/l) may be life-threatening (Travis, 1996:1331).

1.3.2 Magnitude of plasma sodium and potassium disturbances in diarrhoeal disease globally

Hypernatraemia (plasma sodium >150 mmol/l) is more prevalent in the developed world (from 19% to 63%) than in the developing world (from 1.5% to 21%) (Paneth, 1980) (Table 1.1). The prevalence of diarrhoea-related hyponatraemia and hypokalaemia are not well reported. Those studies that did report on diarrhoea-related hyponatraemia and hypokalaemia were performed in developing world settings. Three studies were identified that reported prevalence for hyponatraemia in their study populations: one study in Bangladesh reported a 20.8% prevalence (plasma sodium <130 mmol/l) for the duration of 1 year in the general ward of their health complex (Samadi

et al., 1983); one in Cairo reported a 27% prevalence (plasma sodium ≤130 mmol/l) for the duration of 1 month in their oral rehydration ward (Cleary *et al.*, 1981), and one in Zimbabwe reported a 5.5% prevalence (plasma sodium <125 mmol/l) over 7-month period at their paediatric hydration unit in their central hospital (Nathoo *et al.*, 1987).

Table 1.1 Proportion of children (< 4 years old) with dehydrating diarrhoea with hypernatraemia

	Location of study	Hypernatraemia (%)	Source, year published
Developed countries	Manchester, UK	63	Ironside *et al.*, 1970
	Leeds, UK	60	Chambers & Steel, 1975
	Buffalo, USA	34	Bruck, 1969
	Manchester, UK	30	±Macaulay & Blackhall, 1961
	Baltimore, USA	25	Finberg & Harris, 1955
	New York, USA	25	Rosenfeld *et al.*, 1977
	Seattle, USA	23	Skinner & Moll, 1956
	Chicago, USA	21	DeYoung & Diamond, 1960
	Cleveland, USA	20	Weil & Wallace, 1956
	Manchester, UK	19	Jacobs *et al.*, 1970
Developing countries			
	Nigeria	21	Ahmed & Augusto-Odutola, 1970
	Saudi Arabia	12.6	Karrar & Abdullah, 1981
	Egypt	10	Fayad *et al.*, 1992
	Zimbabwe	8.9	Nathoo *et al.*, 1987
	South Africa	*8	Prinsloo & Kruger, 1970
	Bangladesh	6.4	Samadi *et al.*, 1983
	Saudi Arabia	4.8	Mehasi & Murthy, 1990
	South Africa	3.8	Beatty *et al.*, 1974
	South Africa	3.8	±Hill *et al.*, 1981
	South Africa	¤1.5	Kassel *et al.*, 1970

Serum sodium levels greater than ¤145 mmol/l and *144 mmol/l (Part of table extracted from Paneth, 1980).

±Age range not reported or unclear.

Two studies were identified that reported the prevalence of hypokalaemia in their study populations recruited over a 7-month period: one study performed in Bangladesh reported a prevalence of 67.1% (potassium <4 mmol/l) at the International Centre for Diarrhoeal Disease Research (Zaman *et al.*, 1985), and another performed in Zimbabwe reported a 27.5% prevalence (potassium <3 mmol/l) at their paediatric hydration unit in the central hospital (Nathoo *et al.*, 1987).

1.3.3 Magnitude of plasma sodium and potassium disturbances in the study setting

Analysis of routine laboratory records of children admitted to the Red Cross Children's Hospital's Rehydration Unit in Cape Town, from 1995 to 1997 revealed that 11% had plasma potassium levels below 2.5 mmol/l, 3% had plasma potassium levels below 2 mmol/l, and 7% had plasma sodium levels above150 mmol/l, with 1.8% being severely affected (>158 mmol/l) (unpublished).

1.4 Purpose statement

The purpose of the current research was to explore factors that could contribute to electrolyte disturbances in children with diarrhoea, specifically plasma sodium and potassium disturbances. Possible determinants of these electrolyte disturbances were explored as well as issues surrounding management and diagnosis of the disturbances.

1.5 Rationale for this research project

The high prevalence of these potentially harmful plasma sodium and potassium disturbances at the Red Cross Children's Hospital and in other settings raised a number of issues around i) prevention, ii) the ability to identify the disturbances when they do occur, and iii) management of them once they have been identified. These issues will be addressed in three

separate research studies. The three research studies and their rationale will be described in the sections 1.5.1 to 1.5.3 below.

1.5.1 Determinants of plasma sodium and potassium disturbances in childhood diarrhoea

Identification of aetiological factors in the development of electrolyte disturbances could inform public health interventions to prevent the development of such disturbances. An exploratory analysis of routine laboratory records over 2 years at Red Cross Children's Hospital revealed a striking seasonal variation in mean concentrations of plasma sodium and potassium, with lower levels of both electrolytes in summer and a possible socio-economic gradient in levels when analysed by postal code. The fluctuations did not appear to be due to sampling bias (see glossary) from admission or testing practices (Swingler & Power, 2002). These findings suggested that determinants of these electrolyte disturbances could also be seasonal in their distribution.

The clinical importance of these seasonal fluctuations has been reported in a previous study (Swingler & Power, 2002) in which the prevalence ratio for severe hypokalaemia (<2.0 mmol/l), in February compared with August of 18 (7.2% vs 0.4%), and for severe hypernatraemia (>160 mmol/l) of 0.08 (0.4% vs 5.0%). These fluctuations thus accounted for approximately a 10- to 20-fold variation in the prevalence of severe electrolyte disturbances and highlights the importance of identifying factors that could be associated with these *seasonal fluctuations* and that could result in prevention of these disturbances. The determinants appear to be operating in the whole population of children with diarrhoea, with an important 'spill-over' into abnormally high sodium levels in winter, and abnormally low potassium levels in summer.

In this study, factors that could be associated with the *seasonal fluctuations* previously observed in plasma sodium and potassium levels in childhood diarrhoea will be investigated.

1.5.2 Clinical signs of plasma sodium and potassium disturbances in childhood diarrhoea

Electrolyte disturbances in childhood diarrhoea are usually easily corrected once detected, but detection requires laboratory measurement. Facilities for the measurement of electrolyte levels are seldom available in settings where children are treated for diarrhoea in the developing world. It is therefore important to identify children with suspected electrolyte disturbances so that they can be referred for confirmation and management of the abnormality.

The identification of simple clinical features that accurately identify such children would be very useful. Clinical features of hypernatraemia, hyponatraemia and hypokalaemia are widely accepted, based on case series of children with the disturbances (Chhabra *et al.*, 1995; Kuzemko, 1969). However, no studies have been reported on the diagnostic accuracy of these signs in distinguishing children with electrolyte disturbances from those without disturbances. This study will establish the clinical meaningfulness of those clinical features previously reported to be associated with plasma sodium and potassium disturbances, by assessing their diagnostic accuracy.

1.5.3 Therapeutic impact of routine electrolyte measurement in management of plasma sodium and potassium disturbances in children with diarrhoea

Although facilities to measure electrolytes are seldom available in settings where dehydrating diarrhoea is managed, when such testing is available, they are often routinely used in children admitted with diarrhoea. This is illustrated by the fact that the Standard Treatment Guidelines of the Essential Drugs Programme for hospital level paediatrics in South Africa devotes more

than 25% of the section on acute diarrhoea to the management of electrolyte and acid-base disturbances (Essential Drugs Programme South Africa, 1998:13, 14). This implies the liberal, if not routine, measurement of electrolytes in hospitals in order to detect abnormalities. However, neither the clinical benefit nor the amount of change in clinical management as a result of routine electrolyte testing, in low- and middle-income countries, where diarrhoea is more prevalent has been established.

This study will report on the current management of electrolyte disturbances, identified by routine electrolyte testing, in children with diarrhoea at Red Cross Children's Hospital.

1.6 Outline of thesis

Since the study population, sampling and ethical considerations surrounding data collection for each study were similar and overlapped, an overall description of these is provided in Chapter Two. Details specific to each study are covered in more detail in the particular chapters dealing with them. Chapter Three reports on aetiological factors that are associated with either plasma sodium or plasma potassium disturbances; Chapter Four reports on the diagnostic accuracy of clinical signs used to identify plasma sodium or plasma potassium disturbances; Chapter Five reports on the therapeutic impact of routine electrolyte testing on management of patients and Chapter Six provides a summary of the research and recommendations.

CHAPTER TWO: OVERVIEW OF METHODS

2.1 Objectives

This thesis reports on three separate cross-sectional analytical studies of children with dehydrating diarrhoea that examine different aspects of disturbances of plasma sodium and potassium levels. These are:

a) the clinical, nutritional, microbiological and environmental determinants of seasonal and socio-economic associations with plasma sodium and potassium concentrations,
b) the diagnostic accuracy of clinical signs in the identification of disturbances of plasma sodium and potassium, and
c) the utility of routine plasma sodium and potassium measurement in the clinical management of children with dehydrating diarrhoea.

2.2 Study setting and population

All three studies were performed in the short-stay Rehydration Unit at Red Cross Children's Hospital, Cape Town. This Unit admits approximately 2500 children with dehydrating diarrhoea per year (unpublished data from routine hospital records, 2003-2004). Critically ill children requiring intensive care bypass this Unit, but almost all other children with dehydrating diarrhoeal disease presenting to the hospital are managed there. Medical care is provided according to treatment protocols that provide for the management of electrolyte abnormalities of different severities. The median duration of stay in this Rehydration Unit was 2 days (inter-quartile range 1-3 days) for the duration of this project. The Unit serves large parts of metropolitan Cape Town and receives virtually no referrals from other rehydration units. It thus serves a population of children broadly representative of those admitted to diarrhoeal rehydration units in metropolitan Cape Town.

2.3 Sampling

All three studies were performed simultaneously over a period of 1 year, with overlapping data collection. In order to provide a sample approximately representing seasonal differences in the numbers of admissions in the summer and winter, target enrolment for each month was estimated by using the mean proportion of patients admitted to the Rehydration Unit from 1999 to 2001 for each month.

Systematic sampling was not feasible in the Rehydration Unit, which admitted children 24 hours per day every day. A prospective consecutive sampling technique during specified times was therefore used. The first patient admitted to the Rehydration Unit on each working day that met the inclusion criteria was approached to participate in the project. (The inclusion criteria differed for each study; differences are described under relevant chapters.) Enrolment continued each day until the target number for that day had been enrolled (depending on the study). When enrolment was behind target, all eligible patients were enrolled until the shortfall was made up. Enrolment started each working day at 10h00 and stopped at 18h00. The principal investigator adjusted her working hours to accommodate the revised hours of enrolment.

Enrolment took place over a full year, from 15 April 2002 to 14 April 2003, to include seasonal fluctuations in the incidence and aetiology of diarrhoea. For this study seasons were determined by plasma sodium and potassium fluctuations (Swingler & Power, 2002) rather than by geographical seasons and were categorised as follows: i) November to January as summer, ii) February to April as autumn, ii) May to July as winter and iv) August to October as spring. Patients between 6 weeks and 2 years of age were recruited into the project as planned between 10h00 and 18h00 for the months of April 2002 to July 2002. A review of the project at the end of July showed a persisting shortfall of patients, since in the winter months (June to July) very few patients that met the inclusion criteria were being admitted.

Examination of admission records found that most of the patients were admitted soon after 18h00. For the remainder of the study period (October 2002 to April 2003), patients were recruited between 11h00 and 19h00. Any deviation from this sampling strategy will be described for the different studies in the relevant chapters.

2.4 Ethical considerations

The study was conducted in ways that were consistent with the University of Cape Town's ethical guidelines, the Declaration of Helsinki (World Medical Association, 2000) and the guidelines for the ethical conduct of medical research involving children (Royal College of Paediatrics and Child Health, 2000); and the research was approved by the Research Ethics Committee of the University of Cape Town (ref. 097/2000 - Appendix 2.4). However, as children are a particularly vulnerable group in our society, some issues need particular attention and will be discussed in detail.

2.4.1 Respect for persons

Written informed consent was obtained from the caregiver in his/her choice of language (Appendices 2.1, 2.2, 2.3) before: i) administration of the questionnaire (see Appendices 3.3 and 3.4) and completion of clinical examination chart (see Appendix 4.4); ii) the collection of blood and stool samples that had not already been collected as part of routine clinical care (see Appendix 3.2); and iii) the collection of information on patient management from the patient's folder (see Appendices 5.3 and 5.4).

Caregivers were provided with information in a language of their choice and in lay persons' terms. Consent forms were provided in English, Afrikaans and Xhosa. The principal investigator (fluent in English and Afrikaans) enrolled English- and Afrikaans-speaking caregivers. An interpreter (fluent in Xhosa) assisted with the enrolment of patients with Xhosa-speaking caregivers. The interpreter was provided with information on the studies and had discussion

sessions about the research projects with the principal investigator prior to commencement of the studies. The interpreter also assisted with the translation of the consent form into Xhosa. Any misunderstanding due to language and differences in cultural perceptions were minimized by this process.

Caregivers were given sufficient information on which to decide whether or not to participate in the study, including the research procedure(s) and their purposes. Caregivers were given an opportunity to read the consent form and ask questions. They were told that participation was voluntary and refusal to participate in the studies would not affect the way the child would be treated. A statement offering the caregiver the opportunity to ask questions and to withdraw from the research at any time was included in the consent form and mentioned in the process of obtaining consent.

For caregivers who were illiterate, the study was described in the presence of a witness who was not associated with the research projects, and affirmative consent was indicated by the caregiver making a cross on the consent form that was also signed by the witness, the principal investigator and the interpreter (in the case of Xhosa-speaking caregivers).

A copy of the signed consent form, that also provided information on i) the research procedure(s), ii) their purposes, iii) how consenting to participate in the research projects would impact on the patient, and iv) the contact details of the principal investigator was given to the caregiver (Appendices 2.1, 2.2, 2.3). The caregivers were also given an open invitation to contact the principal investigator if they had any queries regarding the research. More than one medical officer attended to the patient during their stay in the Rehydration Unit. The nature of the shift system and the rotation of staff every few hours in the Rehydration Unit made it difficult to provide a doctor's name on the consent form.

The principal investigator attended the monthly meetings for the staff of the

Rehydration Unit prior to the commencement of the research to inform the staff of the research procedures. While the research was being conducted, she continued to attend these meetings to remind staff about the research procedure(s) and their purpose, and to report on the progress of the research projects. This enabled nursing staff to take a part in discussions of the projects with caregivers, if this was required, during or after the enrolment of patients.

The questionnaire was administered before admission of the patient to the Rehydration Unit (if the caregiver was still waiting for the medical officer on duty to admit the patient) or after the patient was admitted. As the caregivers stayed in the Rehydration Unit for the duration of the patient's stay, administering of the questionnaire after admission was not an imposition on the caregiver's time.

Confidentiality of patient data was maintained by de-linking the patient name from the study number after information was entered into a database.

2.4.2 Beneficence and non-maleficence

The approximately 10- to 20- fold variation in the prevalence of severe electrolyte disturbances between the cooler winter months versus the warmer summer months highlights the importance of identifying factors that could be associated with these *seasonal fluctuations* and which could result in prevention of these disturbances. The possibility of finding feasible and affordable interventions justified the exploratory nature of this study. Either positive or negative findings in the assessment of the reliability and diagnostic accuracy of clinical signs used to identify these electrolyte disturbances have important implications for a common problem in clinical practice, and the therapeutic impact of routine electrolyte testing in the management of the electrolyte disturbances provides important information for planning future research. All of these potential benefits would flow from the single data collection process.

Potential benefits of the research to future patients can be described as i) prevention of electrolyte disturbances if preventative causative factors were identified, ii) avoidance of unnecessary testing if testing of electrolytes resulted in no change in clinical management, iii) routine electrolyte testing of all children if testing were eventually found to produce sufficient clinical benefit to justify its use, given competing priorities for existing resources, and iv) early identification of electrolyte disturbances and treatment thereof if clinical signs were shown to provide accurate diagnosis.

Minimal risk was imposed on the patients as apart from administration of the questionnaire, and collection of stool samples and venesection in the 10% of children who did not have blood taken as part of their usual care, the patients were not treated differently from other patients in any way. Venesection was part of routine hospital care for 90% of the patients and was performed by either the medical officer in the Outpatients' Unit or the Rehydration Unit. Venesection, even for purely research purposes, is regarded as low risk by the Royal College of Paediatrics and Child Health (2000). Psychological costs of this research were distress to the caregiver who often had to leave the examination room during venesection, and the discomfort of venesection to the child. This procedure was performed for research purposes in only 10% of the patients in this study and given the uncertainty around the benefits of blood sampling, the 10% of children could have benefited from this additional procedure.

2.4.3 Justice

The patients, by the nature of their condition, were from a socially disadvantaged group, dependent on the Hospital for their care during the diarrhoeal episode, and thus vulnerable to exploitation. Given these existing burdens, the additional burden of participation in the study might have been better placed on otherwise less burdened groups. However the topics under study related directly to the specific conditions of the patients studied, to the

extent that their socio-economic and other characteristics were a focus of the study. Justice was served in that the benefits of the research would consequently apply most immediately to the community being studied, as well as socially disadvantaged children elsewhere.

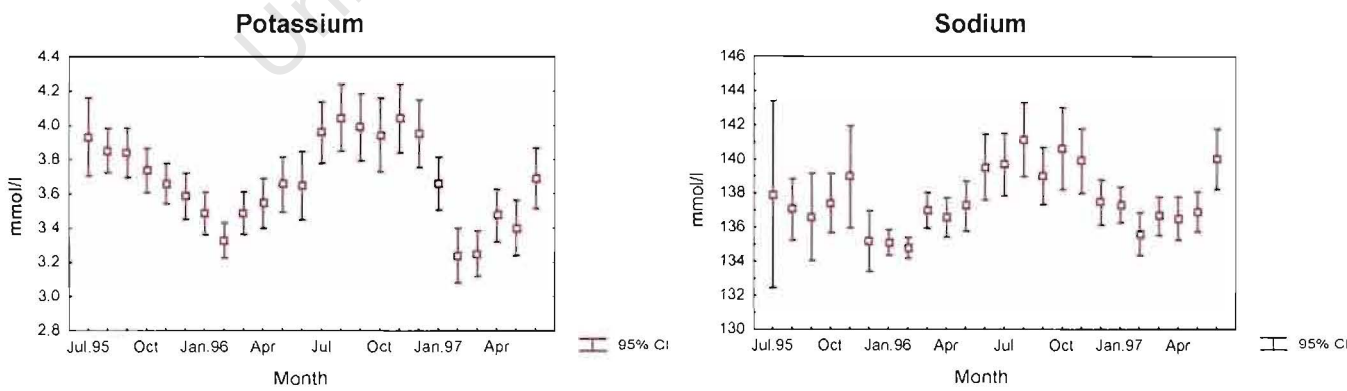
CHAPTER THREE: DETERMINANTS OF SEASONAL FLUCTUATIONS IN PLASMA SODIUM AND POTASSIUM LEVELS IN CHILDHOOD DIARRHOEA

3.1 Background

Globally, plasma sodium and potassium disturbances in children with diarrhoea can result in potentially harmful disorders (Adelman & Solhung, 1996:218; Bruck *et al.*, 1968; Caksen *et al.*, 2001; Finberg, 1986; Mrozowski, 1996:322; Paneth, 1980) and sometimes death (Islam &Khan, 1986; Puffer & Serrano, 1973; Purohit & Jyotsna, 1971; Raghu *et al.*, 1981). The high prevalence of these disturbances at Red Cross Children's Hospital (Rehydration Unit), 7% with plasma sodium >150 mmol/l and 11% with potassium <2.5 mmol/l (unpublished analysis of routine hospital records for the period 1995 to 1999), highlighted the importance of prevention of these disturbances, if possible.

A study performed at Red Cross Children's Hospital reported seasonal variations in the annual distribution of plasma sodium and potassium levels (Swingler & Power, 2002) (Figure 3.1).

Figure 3.1 Mean plasma sodium and potassium levels in dehydrated children with diarrhoea, by season of year (Swingler & Power, 2002).



These findings suggested that determinants of these electrolyte disturbances could also be seasonal in their distribution.

Previous studies have reported seasonal fluctuations of plasma sodium levels in children with diarrhoea, with hypernatraemia more common in winter months (Bruck, 1969; Fayad *et al.*, 1992; Finberg, 1973). The only report of a similar seasonal pattern in plasma potassium levels was the above-mentioned study by Swingler & Power (2002), that reported hypokalaemia as being more common in the summer months. Even though the same seasonal incidence (with a winter peak) observed in Cape Town was reported by Bruck (1969) for hypernatraemia in Buffalo (USA), the Cape Town study had its peak diarrhoea season in summer while Buffalo's peak diarrhoea season was in winter. Bruck (1969) suggested that aetiological and climatic factors were possible contributors to the seasonal incidence of hypernatraemia, but did not elaborate on this.

The fact that similar seasonal fluctuations were identified for plasma potassium as for plasma sodium suggests that a similar mechanism is at work in both, while the existence of similar reported fluctuations of plasma sodium in other countries suggests that the findings of Swingler & Power (2002) are not an artefact of sampling or testing practices.

Potential determinants of these seasonal fluctuations in plasma sodium and potassium levels appear most likely to be those that themselves have a seasonal distribution. Enteropathogens (Table 3.1) have previously been reported to be seasonal in their occurrence in diarrhoea (Pavia, 2004:1446, 1448). In South Africa, enterotoxigenic Escherichia coli (*E. coli*) has been reported to have a summer peak (Coltman, D. 1990. Unpublished research performed at Red Cross Children's Hospital), enteropathogenic *E. Coli* a summer/autumn peak, Shigella and Campylobacter a summer/autumn peak and Rotavirus an early autumn/winter peak (Househam *et al.*, 1988).

Table 3.1 Percentages of enteropathogens in people with diarrhoea in different geographical regions

Organism	Nepal (%)	Asia (%)	India (%)	Latin America (%)	Africa (%)	Peak seasons (Country)
Enterotoxigenic *E. coli*	20-28	0-37	24	26-72	33-71	Summer and autumn (Bangladesh)
Shigella	10-23	0-13	10	0-30	0-15	Summer and autumn (South Africa)
Campylobacter	4-28	*	3	*	5	Summer and autumn (South Africa), winter (Mexico, Morocco)
Salmonella	3	0-33	10	0-16	3	Sporadic through out the year, but less common in summer (South Africa)
Rotavirus	6-11	0-6	5	0-36	6	Early autumn and winter (South Africa)
Cryptosporidium	4	*	2	*	0	-
No pathogen	*	43-94	45	22-83	29-64	-

Results are compiled from studies of varying populations ranging from short-term tourists to military personnel and Peace Corps volunteers. Not all pathogens were sought in all studies. (Part of table taken from Pavia (2004:1446 1448), and compiled from references: Black, 1990; Hoge *et al.*, 1996; Househam *et al.*, 1988; Jiang *et al.*, 2002; Qadri *et al.*, 2000; Taylor *et al.*, 1988).

*Not reported or unclear.

Factors that increase the susceptibility of children to infection with enteropathogens are age, immune deficiency, malnutrition, exposure to unsanitary conditions, a low level of maternal education and infectious diseases (Pickering & Snyder, 2004:1274). Other factors associated with childhood diarrhoea are poor socio-economic conditions, limited access to safe drinking water and poor sanitation (WHO, 2000). Feeding practices in the first year of the life of the child have also been reported to influence the child's susceptibility to diarrhoea, with mixed-fed children being at higher risk of getting the disease than those being breast-fed (Ahiadeke, 2000).

Several factors have been reported as determinants of disturbances of plasma sodium and potassium levels in children with diarrhoea. Hypernatraemia has been reportedly associated with oral rehydration solution (ORS) - either incorrectly prepared or ORS with a high plasma sodium content (Chatterjee *et al.*, 1978; Farthing, 1992; Fayad *et al.*, 1992), better nutrition (Fayad *et al.*, 1992; Samadi *et al.*, 1983), being continually bottle- and breast-fed with limited water intake (Ahmed & Agusto-Odutola, 1970), younger age (Ahmed & Agusto-Odutola, 1970; Hill *et al.*, 1981; Samadi *et al.*, 1983), higher socio-economic status (Yousuf *et al.*, 1988) and parental education (Fayad *et al.*, 1992). Hyponatraemia has been reported to be associated with malnutrition (Samadi *et al.*, 1983), longer duration of diarrhoeal disease (Fayad *et al.*, 1992), and children that are either bottle-fed or are bottle-fed with a weaning diet (Banajeh & Hussein, 1999). Hypokalaemia has been associated with both children that are either bottle-fed or on a bottle and weaning diet (Banajeh & Hussein, 1999), longer duration of diarrhoeal disease (Zaman *et al.*, 1985) and malnutrition (Zaman *et al.*, 1985).

Even though most of the factors mentioned in the previous two paragraphs are not themselves seasonal, they will be investigated because they could be associated with seasonal electrolyte disturbances at the study site by means of confounding factors such as seasonal variation in migration patterns and/or health service utilization, or with climatic variation. Inclusion of such

determinants in the analysis will help to establish their relative importance and adjusted for any confounding effects that may be occurring.

If associations do exist between these factors and the previously observed seasonal fluctuations in plasma sodium and potassium concentrations, they could suggest public health interventions to prevent development of these disturbances.

3.1.1 Review of the literature on the determinants of seasonal fluctuations in plasma sodium and potassium concentrations

3.1.1.1 Identification of relevant studies

A PubMed search (search strategy reported in Appendix 3.1) was performed for the period 1966 to May 2005. Three-hundred and fifty-nine studies were identified in the search. The abstracts of these studies were screened by the principal investigator to identify those that met the criteria of reporting on i) aetiological factors ii) contributing specifically to seasonal fluctuations in iii) plasma sodium and potassium levels iv) in children v) with diarrhoea. Fifty-four studies were deemed possibly relevant and full reports were obtained, to enable fuller assessment. The reference lists of identified studies were also screened for potentially relevant reports.

3.1.1.2 Results of literature review

None of the studies identified in the search met the inclusion criteria detailed in Section 3.1.1.1. Thus no studies investigated factors that could be possible determinants of the *seasonal* fluctuations in plasma sodium and potassium disturbances in children with diarrhoea.

2000). The determinants therefore appeared to be operating in the whole population of children with diarrhoea, causing an important 'spill-over' into abnormal levels.

3.4.2 Sampling

The sampling strategy has been described in section 2.3. In addition, between August 2002 and December 2002, patients admitted the previous evening were enrolled the following morning if electrolytes had been measured on admission and no antibiotics had been administered since admission to the Rehydration Unit. This was done to ensure sufficient numerical representation of stool specimens across seasons. The targeted number of enrolments per month is reported in Table 3.2.

Table 3.2 Targeted enrolment of patients per month

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total
Target	37	46	57	45	33	20	17	15	16	18	20	26	350

3.4.3 Rationale for the selection of hypothesised determinants

The pre-specified independent variables that constituted the hypothesised determinants of seasonal electrolyte disturbances in this prospective study were selected according to the following rationale:

i) Associations with childhood diarrhoea that were themselves seasonally distributed appeared the most likely determinants of seasonal variation i.e. enteropathogens, particularly enterotoxigenic *E. coli*, enteropathogenic *E. coli*, enteroaggregative *E. coli,* Shigella, Salmonella, Campylobacter, Cryptosporidium and Rotavirus.

ii) Socio-economic determinants were of particular interest because of an apparent gradient in the previous study of mean electrolyte levels according

3.2 Aims of the study

The aim of this study was to identify associations, particularly those that were seasonal, with plasma sodium and potassium concentrations in young children admitted to hospital with dehydrating diarrhoea.

3.3 Objectives

a) To confirm by different sampling methods the findings of seasonal fluctuations in plasma sodium and potassium levels reported previously (Bruck, 1969; Fayad *et al.*, 1992; Finberg, 1973; Swingler & Power, 2002).
b) To identify determinants for these seasonal fluctuations.
c) To suggest determinants that could possibly be used to formulate public health interventions to prevent plasma sodium and potassium disturbances.

3.4 Methods

3.4.1 Inclusion and exclusion criteria

Patients between 6 weeks and 2 years of age admitted to the Rehydration Unit during working hours were eligible for this study. Patients were excluded if diuretics were part of the treatment regimen on admission, since these result in the loss of sodium and potassium through urine excretion. Patients residing in the Cape metropolis for less than one month were also excluded as their exposure to their previous environment could still be contributing to their current status.

All patients meeting these criteria were included in the analysis, and not only those with abnormal electrolyte levels as the seasonal variation in a previous study of mean levels for all admissions resulted in approximately a 10- to 20-fold variation in the prevalence of severe disturbances (Swingler & Power,

to the socio-economic status of area of residence (Swingler & Power, 2002). Socio-economic status is an elusive concept involving many inter-related individual and community variables. This study did not attempt to measure wealth *per se*, but rather the association of different socio-economic variables with electrolyte levels. Any such associations could have been direct or indirect using different pathways or they could have been confounding variables. For instance, the availability of piped water may indicate greater wealth, but could also reduce water collection times and make more time available to generate wealth. It could also, by a very different pathway, reduce the opportunity for infection by waterborne diarrhoea pathogens. To have created an index would have been complex, with difficulties in assigning weights to various assets, and potentially counter-productive. Hence it was decided to not construct an index but simply enter all variables individually in a multivariate regression model. This was the approach recommended by Montgomery *et al.* (1997) for use in mortality regressions using DHS data, and was expected to provide more specific and informative results in their analysis. The individual variables included in this study were: availability of electricity, type of stove (electric/or not), type of house (brick/shack), flush toilet (none/off-site/on-site/in-house), piped water (none/off-site/on-site/in-house), use of appliances and parental education. The above factors relating to socio-economic status were chosen because they are known to partly mediate an association with diarrhoea. For instance, ownership of a fridge or deep-freeze would enable food to be kept fresh, and the availability of electricity was necessary to be able to use the appliance. The relationship between diarrhoea, water supply, sanitation (WHO, 2000) and parental education (Ahiadeke, 2000, Mahalanabis *et al.*, 1996) is well established.

iii) Duration of exposure to the local environment, and the degree of urbanisation i.e. duration of current residence, and duration of previous residence was proposed initially. It was planned to use the categorisation of the area of residence in the latest census as a measure of urbanisation, but it was not possible to access the census data due to financial constraints.

iv) Associations with childhood diarrhoea that were not themselves inherently seasonal but which could be associated with seasonal electrolyte disturbances at the study site by means of confounding factors such as seasonal variation in migration patterns and/or health service utilization, or with climatic variation. Such potential associations were: a) clinical determinants (age, gender, weight for height, height for age, duration of diarrhoea, duration of vomiting, adequacy of drinking, persistent diarrhoea, shock, co-morbidity, degree of dehydration, HIV status); b) treatment before admission (source of primary contact care, use of oral rehydration solution, other remedies); and c) diet (breast milk, any other type of milk, solids or semi-solids, sodium content of milk).

v) Plasma pH, which affects particularly plasma potassium concentrations.

3.4.4 Measurement of outcomes and data collection

The medical officer on duty performed venesection on admission, either in the Outpatients' Unit or the Rehydration Unit.

Dependent variables

Plasma sodium and potassium concentrations were measured by the hospital's routine clinical laboratory using the direct ion-electrode method. The principal investigator extracted electrolyte results from computerised laboratory records (Appendix 3.2).

Independent variables and potential confounding factors

a) Clinical determinants:

- *Age** (per completed month),

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* Extracted from routine clinical records from the principal investigator. The routine clinical records are structured to lend themselves to data extraction (see Appendix 5.3).

- *Gender** (male, female),
- *Weight** (kilograms) *for height*‡ (centimetres) as a measure of wasting (Z-score),
- *Height*‡ (centimetres) *for age** (per completed month) as a measure of stunting (Z-score),
- *Duration of diarrhoea*¶ (per completed day),
- *Duration of vomiting*¶ (per completed day),
- *Adequacy of drinking*¶ (not drinking at all/drinks less than normal/ drinks more than normal/drinks normally)
- *Persistent diarrhoea*¶ (number of previous admissions for diarrhoea),
- *Presence of shock** (yes/no),
- *Presence of co-morbidity** (yes/no),
- *Degree of dehydration* ([{discharge weight – admission weight}/discharge weight] X100),
- *Known HIV status** (positive/negative/exposed [defined as having a positive ELISA test and being under 18 months of age or mom is positive]/unknown).

b) Treatment before admission:

This was assessed by asking the caregiver if s/he had sought health care from any person for the current diarrhoeal episode. It was decided to record type of health care before admission rather than medications administered (other than oral rehydration therapy), as caregivers were presumed more likely to remember who they visited than the actual medications. Variables assessed were:

- *Source of primary contact care*¶ (allopathic/or not),

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* Extracted from routine clinical records from the principal investigator. The routine clinical records are structured to lend themselves to data extraction (see Appendix 5.3).

‡ Measured by the principal investigator. Length was measured with a measuring board.

¶ Measured by a pre-piloted questionnaire administered by the principal investigator (Appendices 3.3 and 3.4).

- *Other remedies*[¶] (any visits made to a traditional healer and/or any other practices including home remedies),
- *Oral rehydration solution*[¶] (was any administered prior to admission and if so the type).

c) Biochemical determinants:

Plasma pH was recorded only if the test was done as part of routine testing on admission to the Rehydration Unit. It was regarded as unethical to perform venesection again only to test pH if not needed for clinical management. The principal investigator extracted pH results from laboratory records (Appendix 3.2).

d) Microbial determinants:

The first stool passed by the patient after enrolment into the study was collected to establish the presence or absence of the following enteropathogens by stool culture in the routine clinical laboratory:

- *Shigella* (yes/no),
- *Salmonella* (yes/no),
- *Campylobacter* (yes/no),
- *Cryptosporidium* (yes/no),
- *Rotavirus* (yes/no),
- *ETEC* [enterotoxigenic *E. coli*] (yes/no),
- *EPEC* [enteropathogenic *E. coli*] (yes/no),
- *EHEC* [enterohaemorrhagic *E. coli*] (yes/no),
- *EAEC* [enteroaggregative *E. coli*] (yes/no).

If stool samples were not collected by the time the principal investigator left,

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[¶] Measured by a pre-piloted questionnaire administered by the principal investigator (Appendices 3.3 and 3.4).

the nurses on night duty and the caregivers of patients participating in the study were informed that the first stool passed by the patient needed to be collected. The principal investigator followed through the next morning with the laboratory to ensure that the stool sample was collected and sent for analysis. The principal investigator extracted electrolyte and stool results from laboratory records (Appendix 3.2).

Methods used to identify the different enteropathogens are described in Appendix 3.5.

e) Diet:

This was assessed by asking the caregiver if the patient was receiving nutrition from:

- *Breast milk*[¶] (yes/no),
- *Any other type of milk*[¶] (yes/no),
- *Solids or semi-solids*[¶] (yes/no),
- *Plasma sodium content of milk* (mg/100 ml) was determined by taking the average plasma sodium content of the types of milk that were part of the patients' diet (Van der Spuy, D. 2003. Personal Communication. 29 July, Red Cross Children's Hospital, Cape Town). The sodium content in the different formula feeds was provided by the Dietetics Unit at Red Cross Children's Hospital.

f) Socio-demographic determinants:

- *Duration of current residence*[¶] (months), representing an exposure to a current environment,
- *Previous residence*[¶] (yes/no), representing exposure to previous environment,

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[¶] Measured by a pre-piloted questionnaire administered by the principal investigator (Appendices 3.3 and 3.4).

- *Duration of previous residence*[¶] (months).

g) Socio-economic determinants:

- *Electricity*[¶] (yes/no),
- *Type of stove*[¶] (electric/or not),
- *Type of house*[¶] (brick/shack),
- *Flush toilet*[¶] (none/off-site/on-site/in-house),
- *Piped water*[¶] (none/off-site/on-site/in-house),
- *Appliances*[¶] (no electricity and no appliance (fridge or deep-freeze)/ electricity but no functional appliance/electricity and a functional appliance),
- *Parental education*[¶] (the highest grade achieved by the parent present during admission; one unit increase was attributed above grade 12 for every year of post-matric education successfully completed).

3.4.4.1 Pilot study

A pilot study was performed to assess the clarity of the questionnaire administered to the caregivers (Appendices 3.3 and 3.4). A small number of participants was deemed sufficient to establish this. Six caregivers from different areas (Khayelitsha, Parow, Parow Valley, Bishop Lavis, Goodwood and Thornton) speaking either English, Afrikaans or Xhosa completed the questionnaire with the assistance of the principal investigator. The Xhosa-speaking caregiver included in the pilot preferred to speak English.

3.4.4.2 Blinding

Microbiological and electrolyte investigations were performed in different laboratories by different staff. The principal investigator, who administered

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[¶] Measured by a pre-piloted questionnaire administered by the principal investigator (Appendices 3.3 and 3.4).

the questionnaires, was not blinded to the electrolyte results.

3.4.5 Analysis

Associations between each independent variable and plasma sodium and potassium concentrations were first assessed individually by simple linear regression. Variables with statistically significant associations ($p<0.10$) with potassium or plasma sodium concentrations in the bivariate analyses were further assessed for associations ($p<0.05$) in multiple linear regression analysis. Mean substitution was performed on variables with less than 5% missing observations. Sensitivity analyses i) excluding variables with more than 5% of observations not reported; and ii) excluding patients enrolled that were admitted the previous night (see interim sampling strategy) were performed on multiple regression analysis.

Colinearity between independent variables was determined by calculating the variance inflation factor (VIF). Variables with a VIF >10 were considered as colinear. These variables were tested individually in multiple regression analysis. The variable in the regression analysis with the higher mean VIF was included in the final regression model.

The normality of the distribution of the residuals in the final regression analysis was assessed by the Sharpiro-Wilks test for normally distributed data ($p>0.05$).

Potential effect modifiers of associations with plasma sodium or potassium concentrations were assessed by testing for interactions with the following variables in the regression models: age, nutritional status (Z-scores for height for age, and weight for height) and the degree of dehydration.
The planned number of determinants assessed, including individual enteropathogens, was 35. Using the rule of thumb of a minimum of 10 cases required for each determinant assessed (Altman, 1991:349), approximately 350 patients were required for analysis.

Data were managed using the Access 2000 program (Microsoft Corporation, 1992-2001). Z-scores or nutritional variables were calculated using Epi Info 2000 (version 1, US Centers for Disease Control and Prevention). Simple and multiple linear regression analysis were done using Stata 7.0 (Stata Corporation, 1984-2001).

3.5 Results

A total of 2270 patients were admitted to the Rehydration Unit from 1 April 2002 to 31 March 2003 (data from unpublished routine hospital records). Three-hundred and ninety-seven patients were enrolled into the study over a closely related one-year period (15 April 2002 - 14 April 2003). Of these, 350 (88.2%) patients who had complete demographic data and produced a stool specimen were included the final analysis (Figure 3.2). The number of patients enrolled per month, together with the percentage of total admissions enrolled per month, are presented graphically in Figure 3.3 and 3.4. Figure 3.3 shows a marked seasonal increase in numbers in the late summer and early autumn months as was observed by Swingler & Power (2002). Similar proportions of people were sampled during the various months except for the months between May and June (Figure 3.4). The mean plasma sodium and potassium concentrations per month are graphically displayed in Figure 3.5 and the distribution of the concentrations for the duration of the study in Figure 3.6. A very similar distribution of mean plasma sodium and potassium as reported by Swingler & Power (2002) was observed (though with broader 95% CI) (Figure 3.5). Sodium had a mean concentration of 138 mmol/l (standard deviation of 9.7mmol/l) and potassium had a mean concentration of 3.5 mmol/l (standard deviation of 1.0 mmol/l) (Figure 3.6).

Figure 3.2 Profile of enrolment – determinants of the seasonal fluctuations in sodium and potassium concentrations

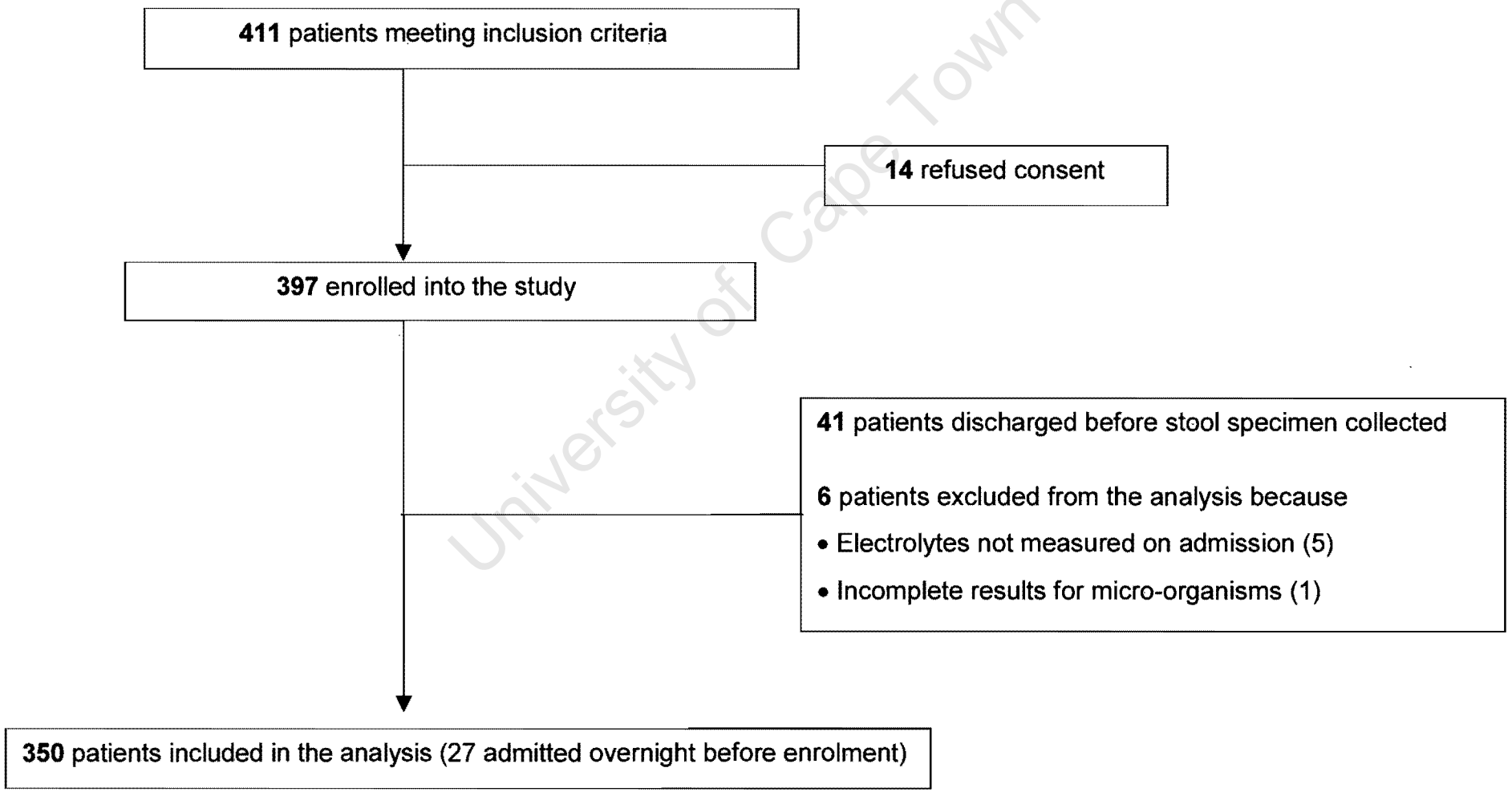
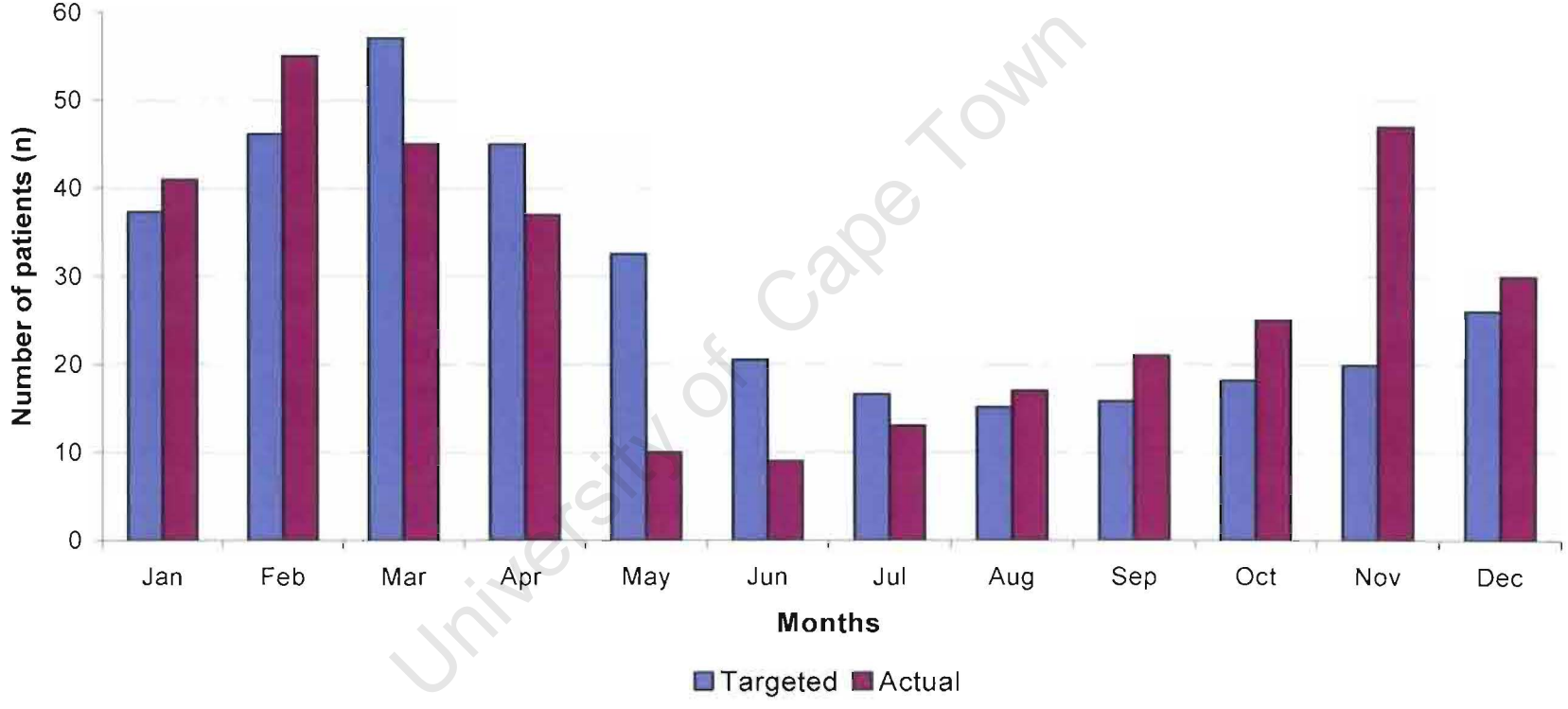


Figure 3.3 Distribution of the targeted and actual enrolments of patients per month for the duration of the study (N=350)



	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Targeted	37	46	57	45	33	20	17	15	16	18	20	26
Actual	41	55	45	37	10	9	13	17	21	25	47	30

Figure 3.4 Percentage of total Rehydration Unit admissions per month enrolled into the study

Figure 3.5 Mean sodium and potassium concentrations (mmol/l) per month

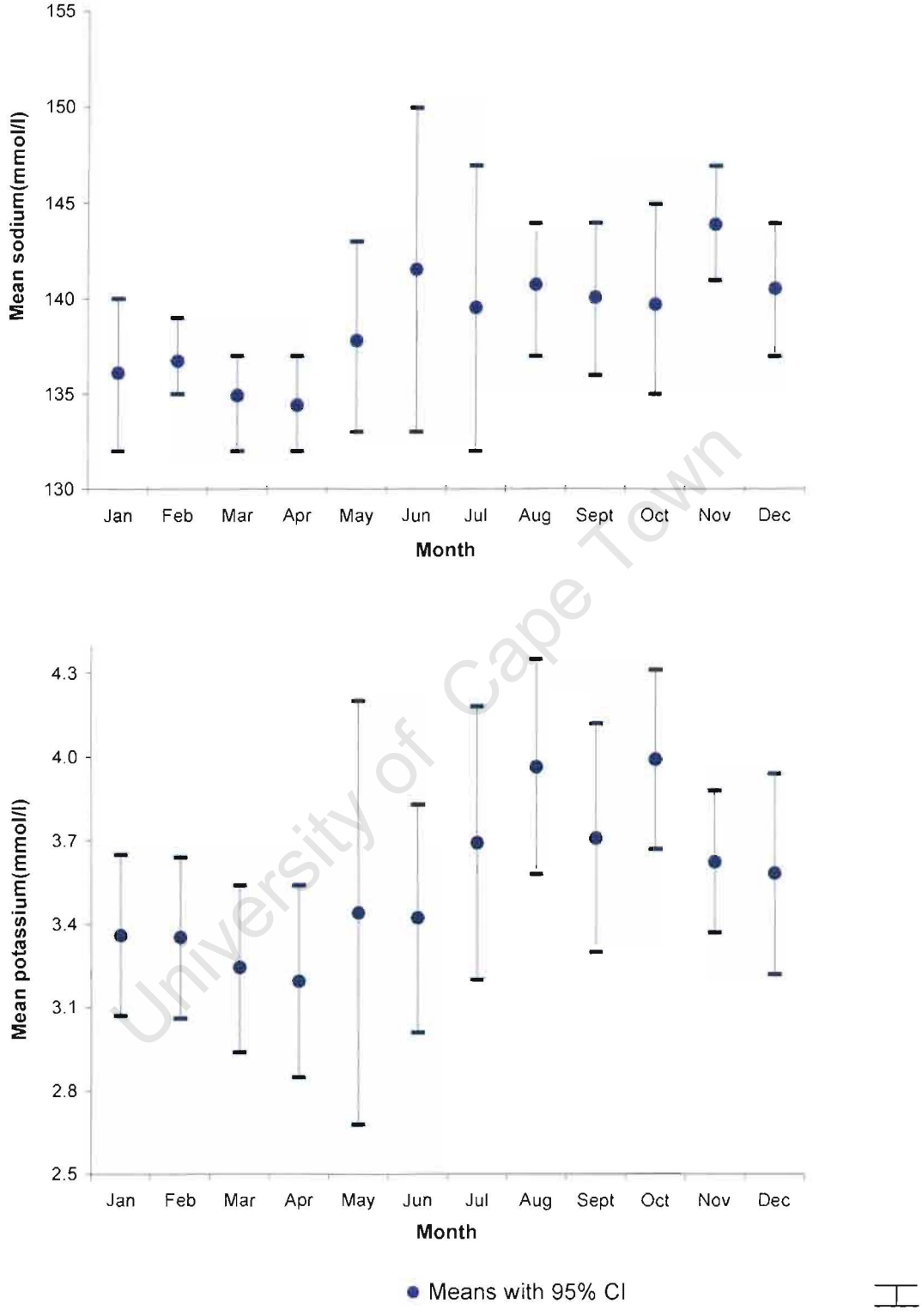
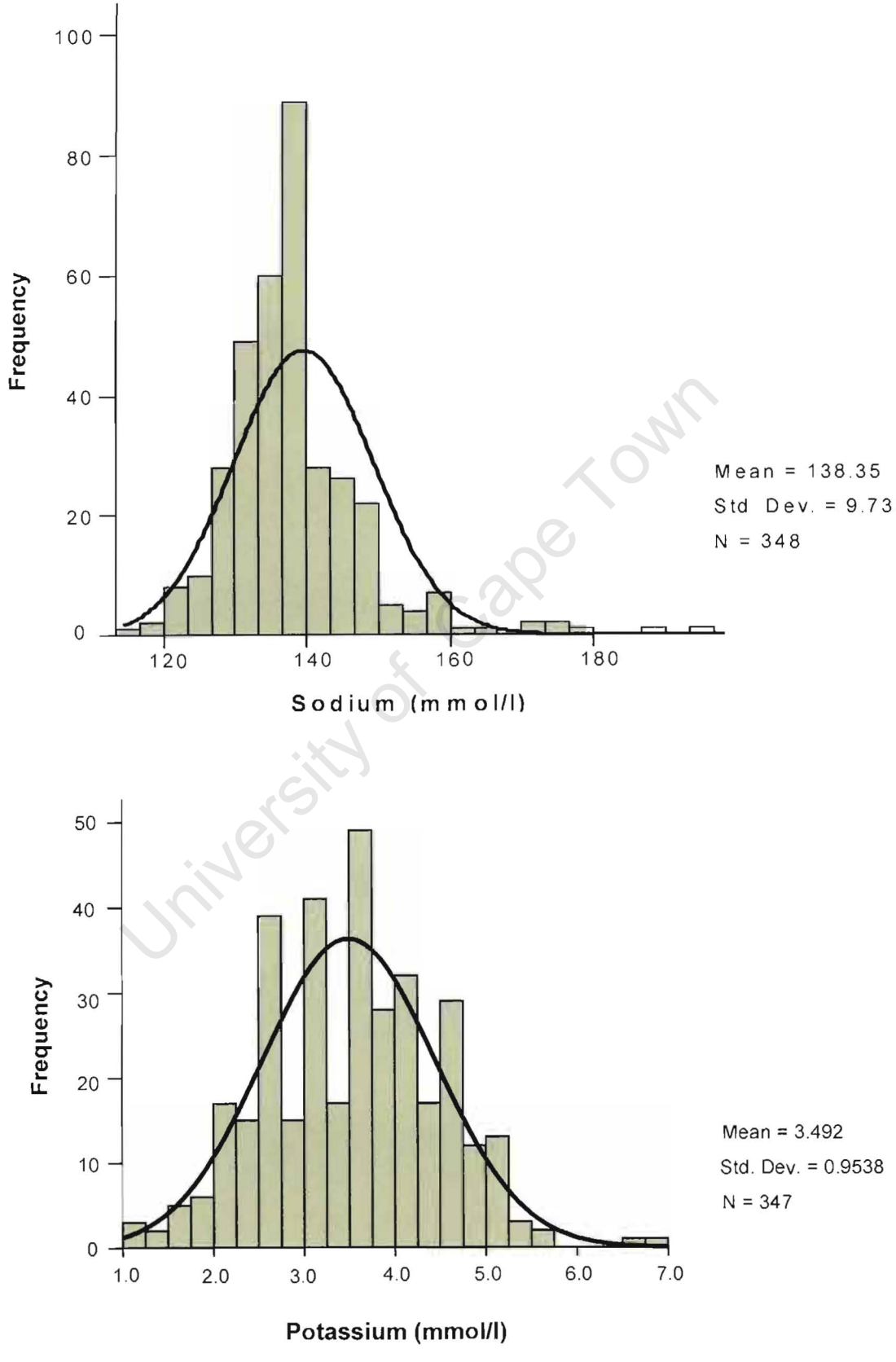


Figure 3.6 Distribution of plasma sodium and potassium concentrations (mmol/l)



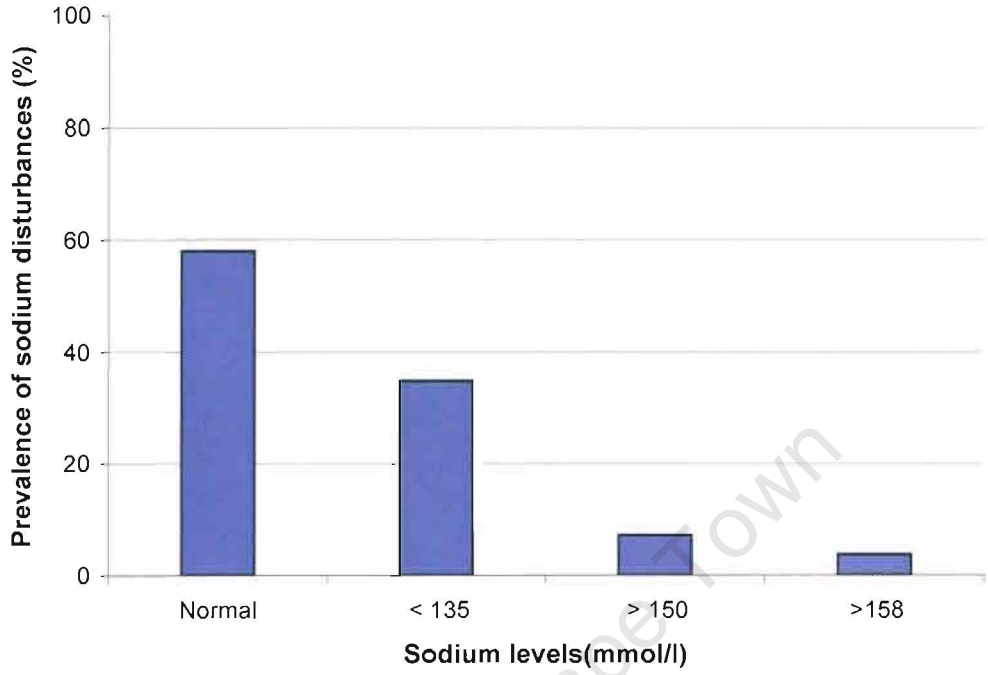
Of the 348 patients with plasma sodium results available, 121 (34.8%) were hyponatraemic (<135 mmol/l), 25 (7.2%) hypernatraemic (>150 mmol/l); and 13 (3.7%) severely hypernatraemic (>158 mmol/l). Of the 347 patients with plasma potassium results available, 160 (46.1%) were hypokalaemic (<3.5 mmol/l) and 48 (13.8%) severely hypokalaemic (<2.5 mmol/l) (Figure 3.7). More patients, 255 (72.9%), were enrolled between November and April (summer / autumn) compared to May and October (winter / spring), 95 (27.1%). A similar pattern was observed of all admissions to the unit during the same period i.e. 67.5% (vs. 72.9%; p=0.387) between November and April compared to 32.5% (vs. 27.1%, p=0.141) between May and October.

3.5.1 Characteristics of patients

The median duration of diarrhoea and vomiting was 3.5 days (inter-quartile range 2-7 days) and 2 days (inter-quartile range 1-4 days) respectively. Degree of dehydration had a median of 4.08% (inter-quartile range 1.6% to 7.4%). Enteroaggregative *Escherichia coli* (122; 34.9%) was the most frequently isolated enteropathogen, with Shigella (10; 2.9%) the least frequently isolated. All the enteropathogens isolated had summer peaks in absolute numbers (Figures 3.8 to 3.13). Enterotoxigenic *E. coli*, Cryptosporidium, EAEC and Rotavirus had similar summer peaks in proportions for stool collected per month for the study.

Most of the patients were ≥ 5% dehydrated (62.8%), were either normal or under-weight for age (74.6%) and had not had a prior diarrhoeal episode (80.3%). Other clinical characteristics are reported in Table 3.3.

Figure 3.7 Prevalence of sodium (n=348) and potassium disturbances (n=347)



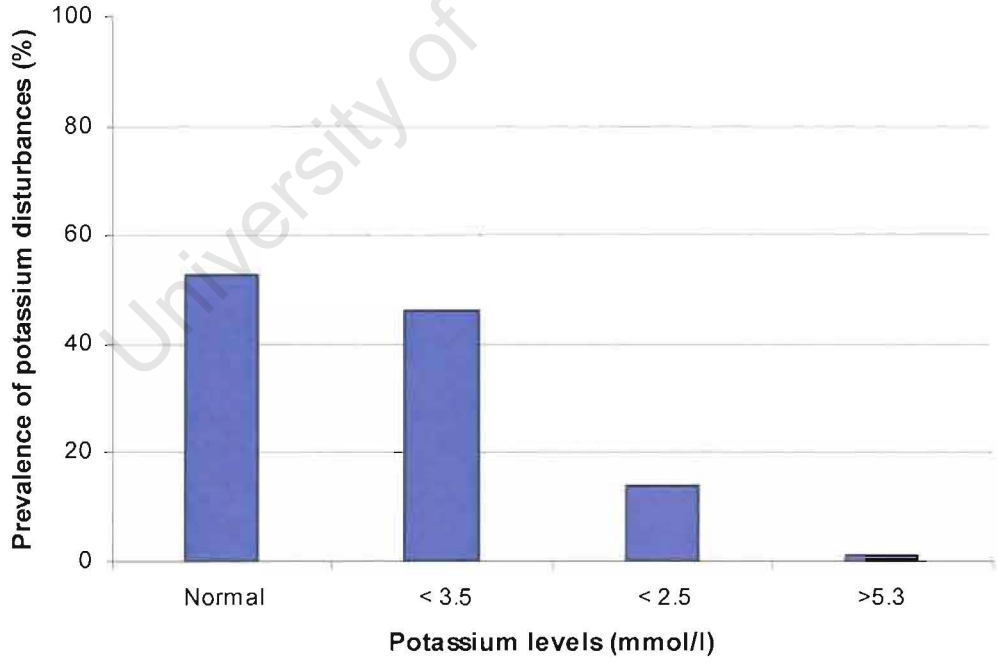


Figure 3.8 **Annual distribution of enterotoxigenic (ETEC) and enteropathogenic (EPEC) *E. coli* associated ($p<0.05$) with sodium concentrations (mmol/l)**

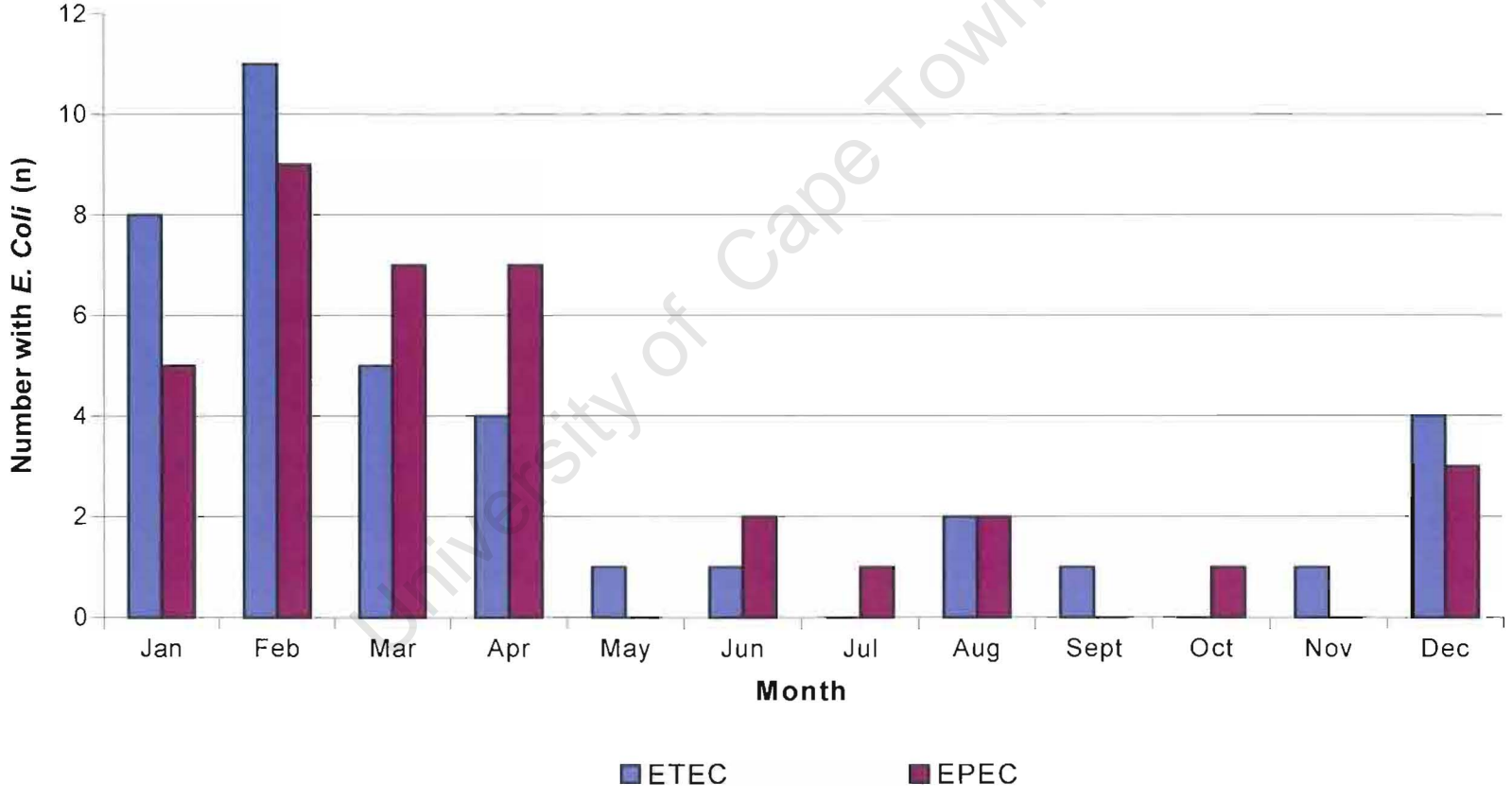


Figure 3.9 Percentage of total stool specimens infected with enterotoxigenic (ETEC) and enteropathogenic (EPEC) *E.coli* per month

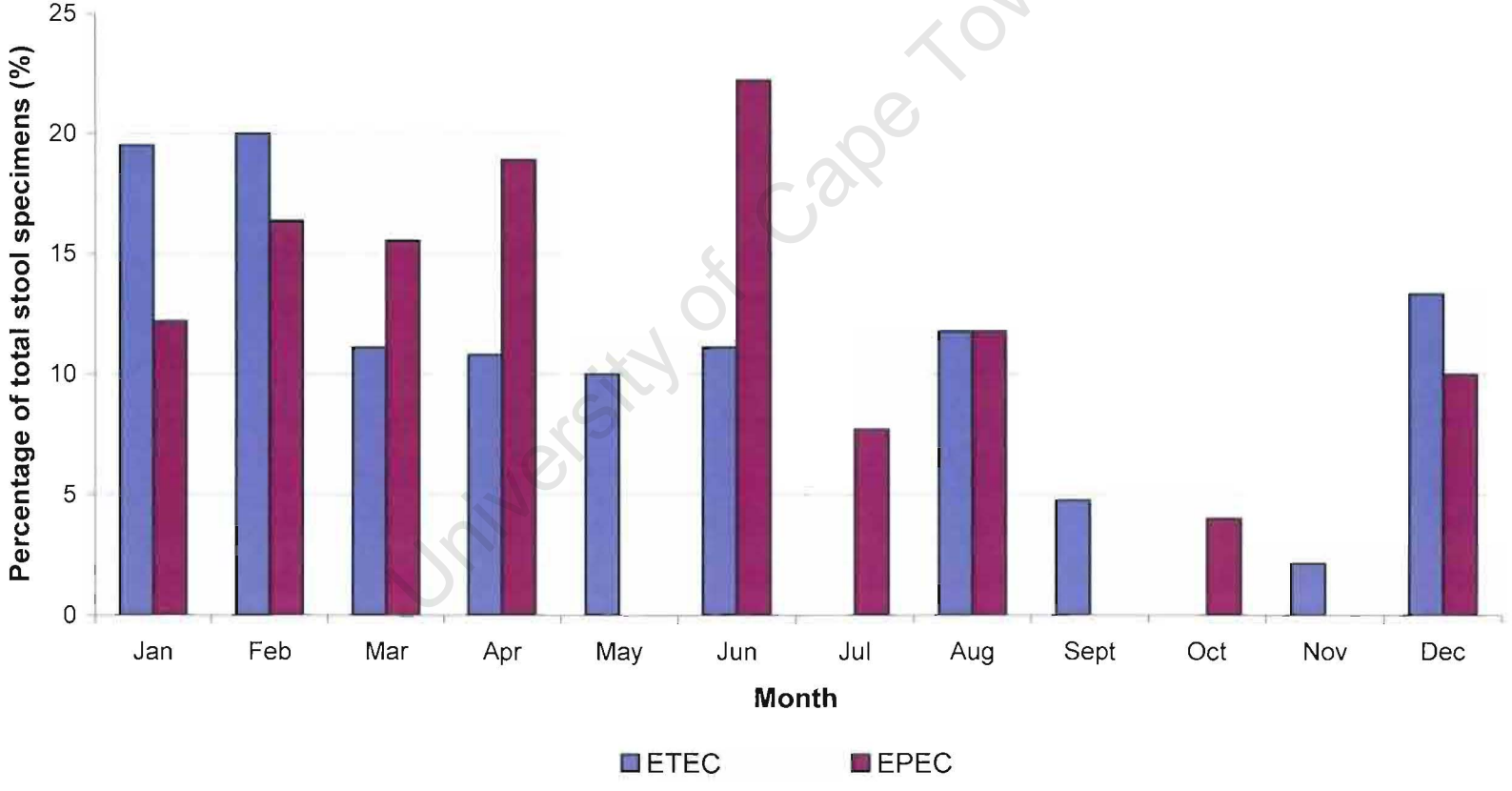


Figure 3.10 Annual distribution of Cryptosporidium (significantly associated, $p<0.05$) with potassium concentrations (mmol/l)

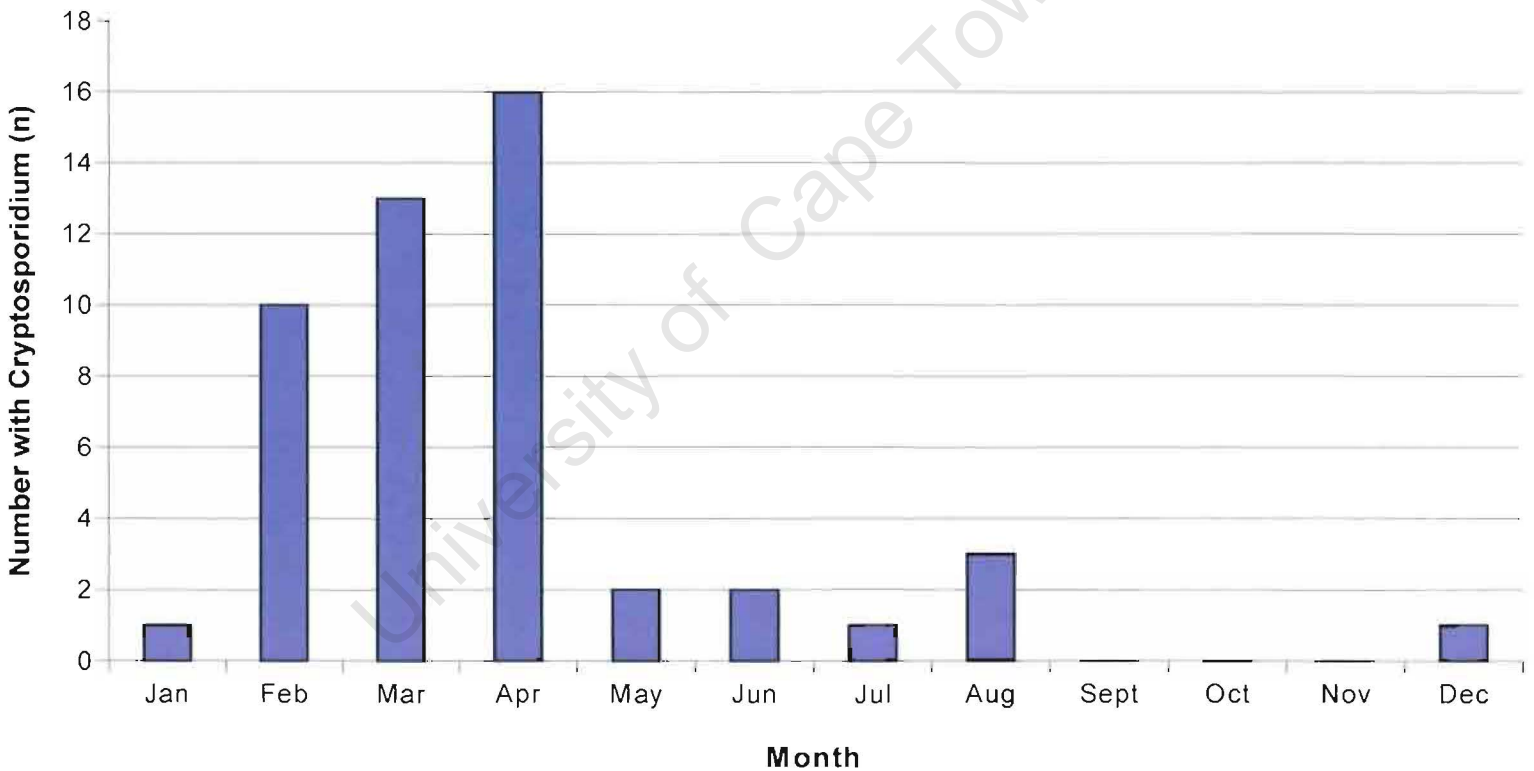


Figure 3.11 Percentage of total stool specimens infected with Cryptosporidium per month

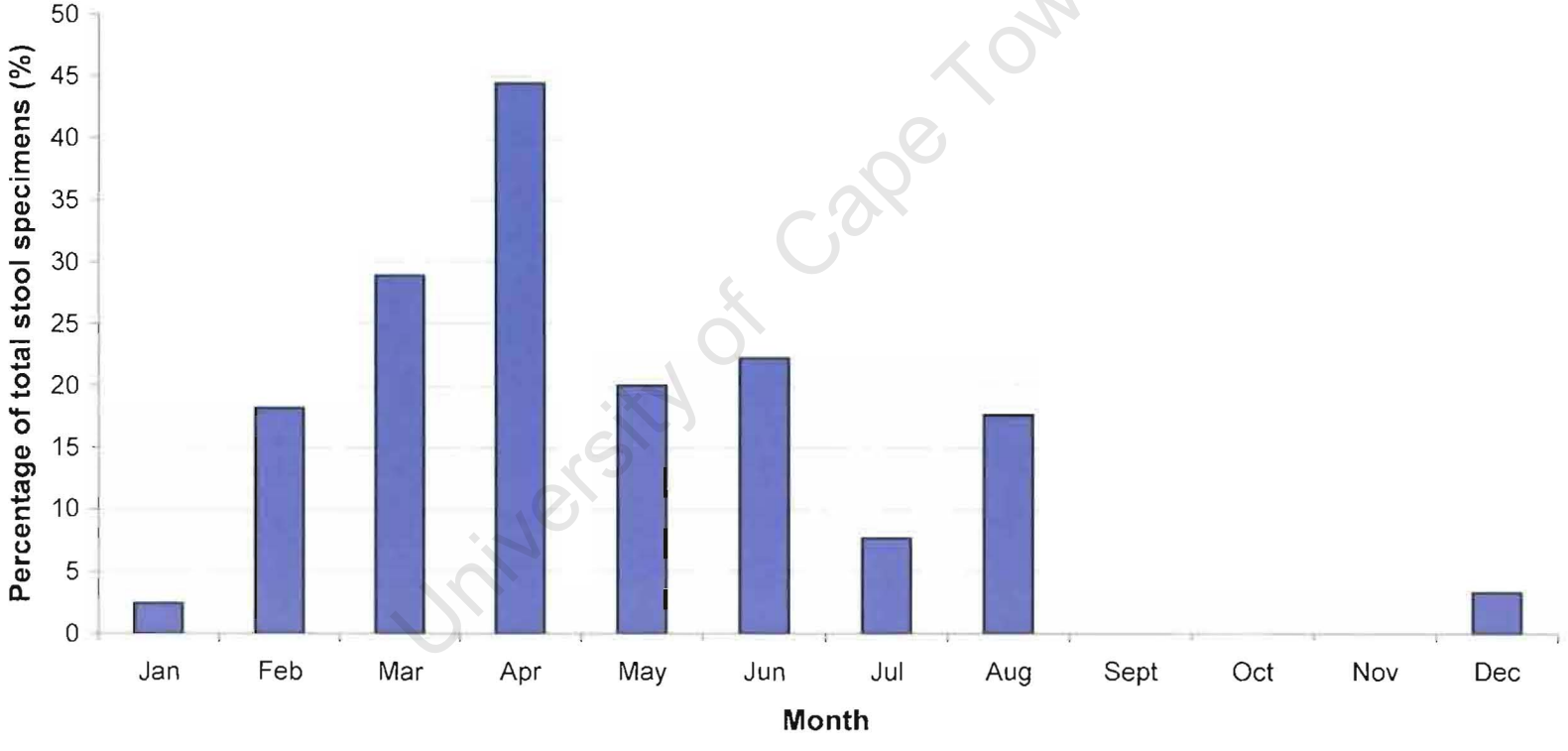


Figure 3.12 Annual distribution of enteropathogens with no statistically significant association ($p>0.05$) with sodium and/or potassium concentrations

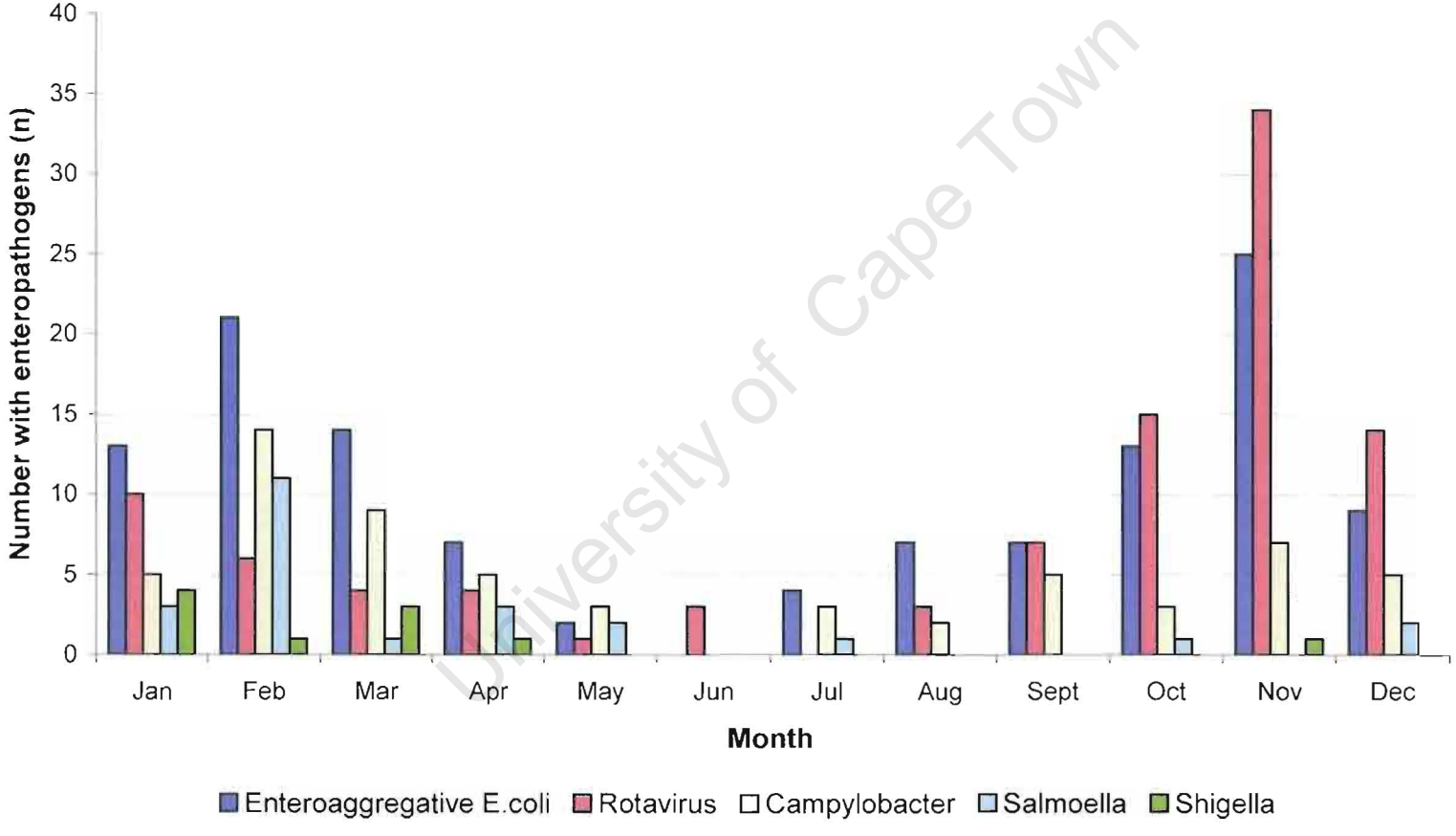


Figure 3.13 Percentage of total stool specimens per month of enteropathogens without a significant association (p>0.05) with sodium and/or potassium concentrations (mmol/l)

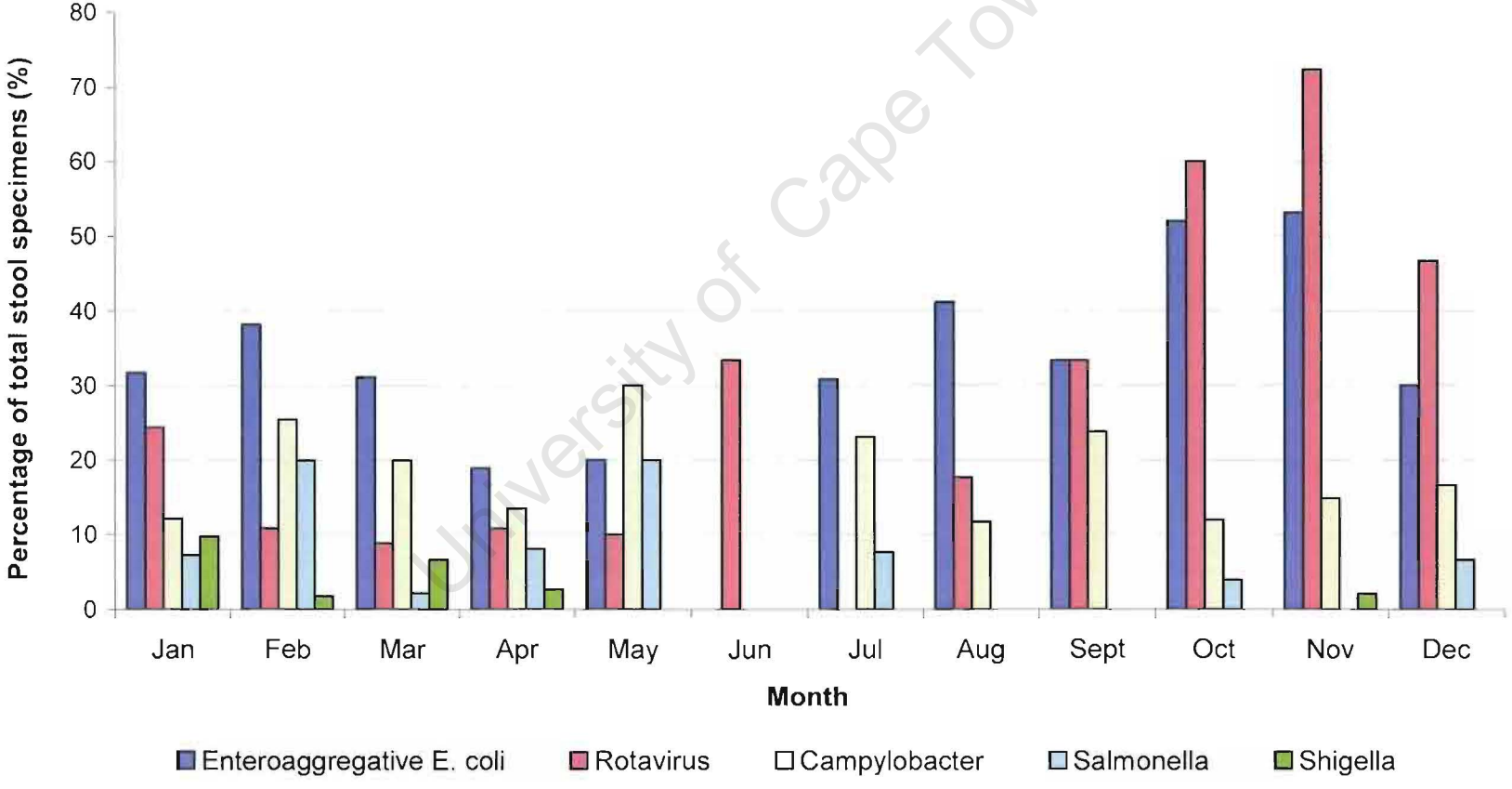


Table 3.3 Percentage distribution of clinical characteristics of patients (N=350)

Microbial aetiology n (%)	***HIV status** n (%)	***Hydration** n (%)	***Peripheral perfusion** n (%)	**Prior diarrhoeal episodes** n (%)	***Severe malnutrion** n (%)
Enteroaggregative *E. coli*	Positive	≥ 10% dehydrated	Poor	Five or more	±Marasmus/kwashiorkor
122 (34.9)	27 (7.7)	54 (15.4)	33 (9.4)	2 (0.6)	41 (11.7)
*Rotavirus	Negative	5% dehydrated	Fair	One to four	±Normal /under-weight for age
101 (28.9)	61 (17.4)	166 (47.4)	118 (33.7)	67 (19.1)	261 (74.6)
*Campylobacter	Exposed	+ Potentially dehydrated	Good	None	
61 (17.4)	47 (13.4)	90 (25.7)	193 (55.1)	281 (80.3)	
*Cryptosporidium		Good hydration			
49 (14.0)		38 (10.9)			
Enterotoxigenic *E. coli*					
38 (10.9)					
Enteropathogenic *E. coli*					
37 (10.6)					
Salmonella					
24 (6.9)					
Shigella					
10 (2.9)					

* Percentage missing data reported in Table 3.5.

+ Potentially dehydrated is defined as no clear sign of dehydration but patient considered to be at risk for dehydration.

± Marasmus and Kwashiorkor were regarded as severe malnutrition. Under weight for age was grouped together with normal weight for age.

More than half (52.7%) of the patients were male. The median age was 8.5 months (inter-quartile range 5-13 months). The median duration of current residence and previous residence was 7 months (inter-quartile range 4-12 months) and 4 months (inter-quartile range 2-8.5 months) respectively. Most of the caregivers had some form of secondary education (78.3%) (Table 3.4). Other socio-demographic and socio-economic characteristics of the patients are reported in Table 3.4.

The diet of 308 (88%) of the patients contained solids or semi-solids, 104 (29.7%) breast-milk and 298 (85.1%) any other type of milk. Allopathic care was reported as the primary source of contact for the current episode of diarrhoea in 295 (84.3%) of the patients, general practitioners (32.7%) being most commonly visited. Most patients (70.9%) had received oral rehydration solution (salt and sugar solution) prior to admission.

3.5.2 Regression analysis

A total of 348 (99.4%) and 347 (99.1%) patients were included in the final analysis of plasma sodium and potassium levels respectively. Mean substitution was performed before multiple regression analysis for the variables parental education, piped water, flush toilet, hydration, peripheral perfusion, pH and Rotavirus, Cryptosporidium and Campylobacter since these variables had less than 5% of their observations missing. Severe malnutrition (48; 13.7%) and presence of co-morbidity (113; 32.3%) had more than 5% of observations missing (Table 3.5).

Table 3.4 Percentage distribution of socio-demographic and socio-economic characteristics of patients (N=350)

*Parental education (level) n (%)	Appliances n (%)	House type n (%)	Type of stove n (%)	*Access to piped water n (%)	*Access to flush toilet n (%)
None	No electricity, fridge or deep-freeze	Shack	No Stove	None	None
4 (1.1)	67 (19.1)	159 (45.4)	2 (0.6)	0	87 (24.9)
Primary – grade 1 to 7	Electricity but no functional appliance	Brick	+Other	Off-site	Off-site
50 (14.3)	81 (23.1)	191 (54.6)	150 (42.9)	92 (26.3)	27 (7.7)
Secondary – grade 8 to 12	Electricity and a functional appliance		Electric	On-site	On-site
274 (78.3)	202 (57.7)		198 (56.6)	101 (28.9)	90 (25.7)
Tertiary – higher than grade 12				In-house	In-house
22 (6.3)				156 (44.6)	145 (41.4)

*Percentage missing data reported in Table 3.5.

+Paraffin stove (133 [38.0%]); burns wood to cook (2 [0.57%]); gas stove (9 [2.57%]).

Table 3.5 Independent variables with missing observations

Variable	Number of missing observations	% of N= 350
Duration of vomiting (per complete day)	1	0.3
Parental education (grade)	1	0.3
Access to flush toilet	1	0.3
Access to piped water	1	0.3
Breast-fed	1	0.3
Adequacy of drinking	2	0.6
Hydration	2	0.6
Cryptosporidium	2	0.6
Rotavirus	6	1.7
Peripheral perfusion	6	1.7
Sodium content in formula milk (mg Na/100 ml)	8	2.3
Campylobacter	8	2.3
pH	14	4.0
Severe malnutrition	48	13.7
Presence of co-morbidity	113	32.3
*HIV status of child	215	61.4
Shocked	250	71.4
HIV status of mother	251	71.7

* HIV status was unknown as patients were not tested for HIV at the Red Cross Children's Hospital or prior to admission to the hospital

Variables with a statistically significant association (p<0.1) with plasma sodium and potassium on a bivariate analysis are shown in Table 3.6. Variables significantly associated with both plasma sodium and potassium levels were age, duration of diarrhoea, duration of vomiting, breast-fed, house type, flush toilet, piped water, duration of current residence, weight for height, degree of dehydration, plasma pH, Shigella, Rotavirus, Cryptosporidium and ETEC.

3.5.2.1 Colinearity and distribution of the residuals

In the multiple regression analysis with plasma sodium, age and duration of current residence were colinear. The model with age had a higher mean VIF (1.75) compared to duration of current residence (mean VIF=1.73), and age was thus included in the final model. The residuals of the final analysis were not normally distributed (Shapiro-Wilks p=0, adjusted R2 = 0.2787, p=0). Plotting the residuals against the fitted values identified patients with plasma sodium levels above 155 mmol/l as outliers. Locally, such very high plasma sodium levels have been observed to occur with incorrect mixing of oral rehydration solutions with a high plasma sodium content. This was presumed to reflect a different pathophysiological process, and the 17 patients with plasma sodium levels greater than 155 mmol/l were removed from the analysis. This resulted in the residuals of the final regression analysis being normally distributed (Shapiro-Wilks p=0.071). The determinants of the multiple regression analysis of plasma sodium explained a statistically significant proportion (adjusted R^2 = 0.3362, p=0) of the variability in plasma sodium levels.

Table 3.6 Associations (p <0.1) with sodium (n = 348) and potassium (n = 347) on bivariate analysis

	Sodium			Potassium		
Independent variable	**β coefficient**	***p* value**	**n**	**β coefficient**	***p* value**	**n**
Age (months)	-0.563	<0.001	348	-0.023	0.011	347
Duration of diarrhoea (per complete day)	-0.191	0.009	348	-0.030	<0.001	347
Duration of vomiting (per complete day)	-0.189	0.053	347	-0.023	0.020	346
Breast-fed	1.938	0.089	347	0.352	0.001	346
House type (brick/shack)	2.563	0.014	348	0.266	0.010	347
Access to flush toilet	-1.422	0.001	347	-0.114	0.007	346
Access to piped water	-2.319	0.0002	347	-0.139	0.025	346
Duration of current residence (months)	-0.475	<0.001	348	-0.026	0.005	347
Weight for height (Z score)	1.221	0.001	348	0.083	0.027	347
Degree of dehydration	0.277	0.022	348	-0.022	0.064	347
Any other milk	-	-	-	-0.283	0.048	347
Parental education (grade)	-	-	-	0.036	0.069	346
Severe malnutrition	-	-	-	-0.267	0.093	300
Presence of co-morbidity	-	-	-	0.287	0.025	235
Hydration	-	-	-	-0.161	0.006	345
Peripheral perfusion	-	-	-	0.207	0.008	341
Plasma pH	-43.786	0	334	1.354	0.020	333
Shigella	-7.571	0.015	348	0.554	0.070	347
Rotavirus	2.634	0.022	342	0.244	0.033	341
Cryptosporidium	-3.767	0.012	346	-0.582	<0.001	345
ETEC	-3.380	0.043	348	-0.284	0.083	347
EPEC	-5.809	0.001	348	-	-	-
Campylobacter	-3.074	0.027	340	-	-	-
Gender (male/female)	2.613	0.012	348	-	-	-
Persistent diarrhoea	-1.857	0.004	348	-	-	-
Sodium content (mg Na/100 ml)	-0.148	0.001	341	-	-	-
Previous residence	2.903	0.033	348	-	-	-
Duration of previous residence (months)	-0.374	0.039	348	-	-	-

None of the variables were colinear (mean VIF=1.99) in the multiple regression analysis with plasma potassium. The residuals of the final analysis were not normally distributed (Shapiro-Wilks p=0.049, adjusted R^2 = 0.1540, p=0). Plotting the residuals against the fitted values identified a patient with a plasma potassium level of 6.8 mmol/l as the most prominent outlier. After removing this observation, the residuals were normally distributed (Shapiro-Wilks p=0.443). This unusually high level of plasma potassium in diarrhoea also appeared to be an outlier in pathophysiological terms and was thus excluded. The determinants of the multiple regression analysis of plasma potassium explained a statistically significant proportion of the variability in plasma potassium levels (adjusted R^2 = 0.1643, p=0).

3.5.2.2 Multiple regression analysis for plasma sodium

Multiple regression models of variables associated (p<0.1) with plasma sodium in the bivariate analysis are reported in Table 3.7. Statistically significant positive associations (p<0.05) with plasma sodium in multiple regression analysis were being breast-fed and type of house. Statistically significant negative associations with plasma sodium in multiple regression analysis were age, plasma pH, ETEC infection and EPEC infection.

3.5.2.3 Multiple regression analysis for potassium

Multiple regression models of variables associated (p<0.1) with plasma potassium in the bivariate analysis are reported in Table 3.8. Statistically significant positive associations (p<0.05) with plasma potassium in multiple regression analysis were parental education and plasma pH. Statistically significant negative associations with plasma potassium in multiple regression analysis were duration of diarrhoea before admission and Cryptosporidium infection.

Table 3.9 summarises the associations for both plasma sodium and potassium for the multiple regression analysis. Plasma pH had a significant

negative association with plasma sodium and a positive association with plasma potassium.

3.5.2.4 Seasonality

In order to assess potential confounding by factors such as migration patterns and health service utilisation, a post hoc analysis was performed of associations between season and i) age, ii) being breastfed, and iii) house type (for sodium); and i) duration of diarrhoea, and ii) parental education (for potassium).

a) Seasonality for associations with sodium in the multiple regression analysis

A statistically significant association was found between season and i) house type and ii) being breastfed. Patients living in brick houses were more common in the summer months (November to April) than in the winter months (58.8% vs. 43.2%; p=0.010). More patients were being breastfed in the winter months (May to October) than the summer months (38.3% vs. 26.7%; p= 0.040).

No statistically significant association was found between season and age (p=0.230).

b) Seasonality for associations with potassium in the multiple regression analysis

No statistically significant associations were observed between season and i) parental education (p=0.531) and ii) duration of diarrhoea (p=0.110).

Analysis of seasonality of enteropathogens was performed *a priori* (Figures 3.8 to 3.11).

Table 3.7 Multiple regression analysis on sodium (n = 331)

Independent variable	β coefficient	Std error	t	*p* value	95% CI
***Age**	**-0.289**	**0.068**	**-4.21**	**0.000**	**-0.425 to -0.154**
Gender	1.215	0.619	1.96	0.051	-0.004 to 2.435
Duration of diarrhoea (per complete day)	-0.043	0.056	-0.78	0.438	-0.155 to 0.067
Duration of vomiting (per complete day)	0.052	0.075	0.70	0.487	-0.096 to 0.202
Persistent diarrhoea	-0.511	0.384	-1.33	0.184	-1.268 to 0.245
***Breast milk**	**1.914**	**0.767**	**2.49**	**0.013**	**0.404 to 3.425**
Sodium content in milk (mg Na/100 ml)	0.018	0.031	0.56	0.573	-0.044 to 0.080
***Type of house**	**2.659**	**0.929**	**2.86**	**0.005**	**0.829 to 4.488**
Access to flush toilet	-0.363	0.510	-0.71	0.476	-1.367 to 0.640
Access to piped water	0.472	0.773	0.61	0.542	-1.050 to 1.994
Previous residence	1.044	1.225	0.85	0.394	-1.366 to 3.455
Duration of previous residence (months)	0.086	0.163	0.53	0.597	-0.235 to 0.409
Weight for height (Z-score)	0.064	0.238	0.27	0.787	-0.405 to 0.534
Degree of dehydration	0.008	0.077	0.11	0.911	-0.1432 to 0.160
***Plasma pH**	**-22.127**	**4.013**	**-5.51**	**0.000**	**-30.024 to -14.231**
***ETEC**	**-2.129**	**0.969**	**-2.20**	**0.029**	**-4.036 to -0.222**
***EPEC**	**-5.118**	**1.017**	**-5.03**	**0.000**	**-7.119 to -3.116**
Shigella	-2.283	1.844	-1.24	0.217	-5.913 to 1.346
Campylobacter	-0.534	0.833	-0.64	0.522	-2.173 to 1.105
Cryptosporidium	-0.585	0.960	-0.61	0.542	-2.475 to 1.303
Rotavirus	0.559	0.729	0.77	0.444	-0.875 to 1.994
Constant	296.758	29.165	10.17	0.000	239.369 to 354.146

*Significant at the 0.05 confidence level

Table 3.8 Multiple regression analysis on potassium (n = 346)

	β coefficient	Std error	t	*p* value	95% CI
Age	-0.012	0.015	-0.80	0.422	-0.043 to 0.018
***Duration of diarrhoea (per complete day)**	**-0.024**	0.008	**-2.85**	**0.005**	**-0.041 to -0.007**
Duration of vomiting (per complete day)	0.004	0.011	0.43	0.664	-0.017 to 0.027
Breast milk	0.155	0.124	1.25	0.213	-0.089 to 0.399
Any other milk	-0.119	0.156	-0.76	0.446	-0.427 to 0.188
***Parental education (grade)**	**0.043**	**0.019**	**2.26**	**0.024**	**0.005 to 0.081**
Type of house	0.215	0.139	1.54	0.124	-0.059 to 0.490
Access to flush toilet	-0.051	0.078	-0.65	0.517	-0.206 to 0.104
Access to piped water	0.080	0.116	0.69	0.490	-0.149 to 0.310
Duration of current residence (months)	-0.019	0.015	-1.22	0.224	-0.050 to 0.011
Weight for height (Z-score)	0.026	0.036	0.73	0.467	-0.045 to 0.099
Degree of dehydration	0.002	0.011	0.18	0.859	-0.021 to 0.025
Hydration	-0.081	0.065	-1.24	0.216	-0.209 to 0.047
Peripheral perfusion	-0.080	0.084	-0.95	0.340	-0.246 to 0.085
***Plasma pH**	**1.679**	**0.612**	**2.74**	**0.006**	**0.475 to 2.884**
ETEC	-0.200	0.150	-1.33	0.183	-0.495 to 0.094
Shigella	0.524	0.287	1.82	0.069	-0.040 to 1.090
***Crytosporidium**	**-0.334**	0.145	**-2.30**	**0.022**	**-0.621 to -0.047**
Rotavirus	0.125	0.111	1.12	0.262	-0.094 to 0.344
Constant	-8.591	4.472	-1.92	0.056	-17.389 to 0.205

* Significant at the 0.05 confidence level.

Table 3.9 Summary of associations ($p<0.05$) with sodium (n = 331) and potassium (n = 346) on multiple regression analysis

	Sodium				Potassium			
	β coefficient	Std error	*p* value	95% CI	β coefficient	Std error	*p* value	95% CI
Duration of diarrhoea	-	-	-	-	-0.024	0.008	0.005	-0.041 to –0.007
Parental education	-	-	-	-	0.043	0.019	0.024	0.005 to 0.081
Cryptosporidium	-	-	-	-	-0.334	0.145	0.022	-0.621 to –0.047
Plasma pH	-22.127	4.013	0	-30.024 to –14.231	1.679	0.612	0.006	0.475 to 2.88
Age	-0.289	0.068	0	-0.425 to –0.154	-	-	-	-
Breast-fed	1.914	0.767	0.013	0.404 to 3.425	-	-	-	-
Type of house	2.659	0.929	0.005	0.829 to 4.488	-	-	-	-
EPEC	-5.118	1.017	0	-7.119 to –3.116	-	-	-	-
ETEC	-2.129	0.969	0.029	-4.036 to –0.222	-	-	-	-

3.5.2.5 Effect modifiers

Degree of dehydration was found to modify the association of being breast-fed with plasma sodium levels (p=0.020). Patients being breast-fed that were more than 5% dehydrated had a 4.12 mmol/l (p=0.011) increase in plasma sodium concentration compared to those that were less than or 5% dehydrated (β coefficient = 1.07 mmol/l, p=0.230). Height for age, weight for height and age are probable confounding variables and not effect modifiers in the analysis for plasma sodium (Table 3.10).

No effect modifiers were identified for associations with potassium. Degree of dehydration, height for age, weight for height and age are probable confounding variables and not effect modifiers in the analysis for potassium (Table 3.11).

3.5.2.6 Sensitivity analyses

Two sensitivity analyses were performed to assess the effect on multiple regression analysis of a) variables with greater than 5% of missing data; and b) patients enrolled who were admitted the previous night.

a) Missing data

The variables most affected by missing data were severe malnutrition and the presence of a co-morbidity, with only 204 cases consequently being included in the multiple regression analysis for plasma potassium. Sensitivity analyses were performed by doing regression analysis i) in the absence of both variables, ii) with severe malnutrition in the absence of co-morbidity, and iii) with co-morbidity in the absence of severe malnutrition.

Table 3.10 Analysis of pre-specified effect modifiers of associations ($p<0.05$) with sodium in multiple regression analysis

Interaction variable	β coefficient	Std error	t	*p* value	95% CI
Age/age	-0.013	0.010	-1.31	-1.31	-0.033 to 0.006
Age/weight for height	-0.006	0.039	-0.17	0.868	-0.083 to 0.070
Age/height for age	0.025	0.015	1.66	0.098	-0.004 to 0.054
Age/degree of dehydration	-0.024	0.013	-1.82	0.069	-0.050 to 0.001
Breast milk/age	-0.138	0.130	-1.06	0.289	-0.396 to 0.118
Breast milk/weight for height	-0.185	0.471	-0.39	0.69	-1.113 to 0.743
Breast milk/height for age	0.184	0.310	0.59	0.553	-0.425 to 0.794
Breast milk/degree of dehydration	**0.428**	**0.181**	**2.36**	**0.019**	**0.070 to 0.785**
Type of house/age	0.016	0.111	0.15	0.879	-0.201 to 0.235
Type of house/weight for height	0.542	0.453	1.2	0.233	-0.350 to 1.435
Type of house/height for age	0.421	0.320	1.32	0.188	-0.207 to 1.051
Type of house/degree of dehydration	0.067	0.150	0.45	0.655	-0.228 to 0.363
pH/age	0.067	0.641	0.11	0.916	-1.195 to 1.330
pH/weight for height	-2.904	2.915	-1.00	0.320	-8.640 to 2.831
pH/height for age	0.033	0.018	1.79	0.075	-0.003 to 0.070
pH / degree of dehydration	-0.316	0.797	-0.40	0.692	-1.886 to 1.254

Table 3.10 (continued) **Analysis of pre-specified effect modifiers of associations ($p<0.05$) with sodium in multiple regression analysis**

Interaction variable	β Coefficient	Std error	t	*p* value	95% CI
ETEC/age	0.293	0.167	1.75	0.081	-0.036 to 0.622
ETEC/weight for height	-0.545	0.874	-0.62	0.533	-2.267 to 1.175
ETEC/height for age	0.071	0.187	0.38	0.705	-0.298 to 0.440
ETEC/degree of dehydration	0.181	0.216	0.84	0.403	-0.244 to 0.606
EPEC/age	0.006	0.198	0.03	0.900	-0.382 to 0.396
EPEC/weight for height	0.965	0.801	1.20	0.229	-0.611 to 2.541
EPEC/height for age	0.529	0.674	0.79	0.433	-0.796 to 1.855
EPEC/degree of dehydration	-0.297	0.214	-1.39	0.166	-0.720 to 0.124

Table 3.11 Analysis of pre-specified effect modifiers on associations ($p<0.05$) with potassium in multiple regression analysis

Interaction variable	β Coefficient	Std Error	t	*p* value	95% CI
Parental education/age	0.0005	0.003	0.15	0.885	-0.006 to 0.007
Parental education/weight for height	0.005	0.013	0.42	0.672	-0.020 to 0.032
Parental education/height for age	-0.001	0.002	-0.82	0.413	-0.006 to 0.002
Parental education/degree of dehydration	0.0003	0.001	0.29	0.772	-0.001 to 0.002
Duration of diarrhoea/age	-0.0002	0.001	-0.17	0.867	-0.003 to 0.002
Duration of diarrhoea/weight for height	-0.008	0.005	-1.62	0.105	-0.019 to 0.001
Duration of diarrhoea/height for age	-0.004	0.002	-1.56	0.120	-0.009 to 0.001
Duration of diarrhoea/degree of dehydration	-0.002	0.001	-1.93	0.055	-0.005 to 0.00004
pH/weight for height	-0.376	0.436	-0.86	0.389	-1.234 to 0.481
pH/height for age	-0.001	0.002	-0.50	0.619	-0.007 to 0.004
pH/degree of dehydration	0.0002	0.001	0.14	0.888	-0.002 to 0.003
pH/age	0.0512	0.096	0.53	0.596	-0.138 to 0.241
Cryptosporidium/degree of dehydration	-0.041	0.027	-1.52	0.131	-0.095 to 0.0124
Cryptosporidium/weight for height	-0.004	0.115	-0.04	0.97	-0.230 to 0.222
Cryptosporidium/age	-0.001	0.026	-0.07	0.947	-0.053 to 0.049
Cryptosporidium/height for age	-0.090	0.078	-1.16	0.248	-0.243 to 0.063

The sensitivity analysis (Table 3.12) found that duration of diarrhoea (n=346, p=0.005; and n=299, p=0.009), plasma pH (n=346, p=0.006; and n=299, p=0.006) and infection with Cryptosporidium (n=346, p=0.022; n=299, p=0.050) were statistically significant in the larger samples only, with significance increasing as sample size increased. However, the β coefficients were not meaningfully changed. The models that were statistically more powerful, without the variables severe malnutrition and co-morbidity, were thus used. Nutritional status was still represented in the models as height for age and weight for height.

b) Overnight admissions

The findings of multiple regression analysis for plasma sodium and potassium in the absence of the 27 patients recruited from overnight admissions are shown in Table 3.13. No meaningful differences were observed in the β coefficients.

Table 3.12 Sensitivity analysis – variables significantly associated (p <0.05) with potassium with and without severe malnutrition and co-morbidity (multi-regression analysis)

	β coefficient				*p* value			
	n=346	**n=299**	**n=235**	**n=204**	**n=346**	**n=299**	**n=235**	**n=204**
Parental education	0.043	0.041	0.060	0.054	0.024	0.044	0.022	0.046
Duration of diarrhoea	-0.024	-0.022	-	-	0.005	0.009	-	-
Plasma pH	1.679	1.836	-	1.655	0.006	0.006	-	0.037
Cryptosporidium	-0.334	-0.288	-	-	0.022	0.050	-	-
Shigella	-	0.622	-	0.727	-	0.030	-	0.034
Severe malnutrition	-	-0.318	-	-	-	0.046	-	-

n=346 - all determinants with p <0.05 except severe malnutrition and co morbidity; **n=299** - all determinants with p <0.05 except co-morbidity; **n=235** - all determinants with p <0.05 except severe malnutrition; **n=204** - all determinants with p <0.05.

Table 3.13 Sensitivity analysis - comparison of multiple regression analysis of sodium and potassium with and without patients admitted the previous night

	Sodium				Potassium				
	β coefficient		*p* value		Variable	β coefficient		*p* value	
	*n=331	+n=306	*n=331	+n=306		*n=346	+n=319	*n=346	+n=319
Age	-0.289	-0.306	0	0	Parental education	0.043	0.043	0.024	0.032
Plasma pH	-22.127	-23.095	0	0	Duration of diarrhoea	-0.024	-0.022	0.005	0.009
EPEC	-5.118	-4.297	0	0	Plasma pH	1.679	2.135	0.006	0.001
ETEC	-2.129	-1.976	0.029	0.037	Cryptosporidium	-0.334	-0.323	0.022	0.027
Breast-fed	1.914	2.185	0.013	0.006					
Type of house	2.659	2.604	0.005	0.005					

*n - Patients admitted during work hours or overnight; +n- Only patients admitted during work hours.

3.6 Discussion

3.6.1 Interpretation of the principal findings

This study, using a different prospective sampling strategy in a different full year, found a seasonal fluctuation in plasma sodium and potassium concentration very similar to those previously described locally. This excludes a possible sampling artefact in the previous study as an explanation for the findings, and provides strong confirmatory evidence of these seasonal fluctuations (Figures 3.1 and 3.5) (Swingler & Power, 2002).

The analysis included a relatively large number of variables potentially affecting electrolyte levels via different pathways. These variables were of widely differing categories, ranging from enteropathogens to duration of diarrhoea to housing to parental education. Although very different, these categories are inter-related in complex ways. For instance, the infecting enteropathogens can affect the duration of diarrhoea; housing is related to sanitation and water supply which could affect the type and frequency of microbiological infection; and parental education, particularly maternal education, is related among other things to housing and to health-related behaviours that are both indirectly and directly related to diarrhoea. Because of these complex inter-relationships and multiple potential confounding factors, they were grouped together in multiple regression models to adjust for confounding and to identify the variables that were independently associated with electrolyte concentrations.

As described in Section 3.4.3, the broad categories of variables were: i) those that were themselves seasonally distributed i.e. enteropathogens; ii) socio-economic determinants; iii) duration of exposure to the local environment; iv) associations with childhood diarrhoea that were not themselves inherently seasonal but which could be associated with seasonal electrolyte disturbances at the study site by means of confounding factors

such as seasonal variation in migration patterns and/or health service utilization, or with climatic variation; and v) plasma pH, which affects particularly plasma potassium concentrations.

On bivariate (unadjusted) analysis many clinical, socio-economic, socio-demographic, dietary and microbial factors were found to be significantly associated with *both* plasma sodium and potassium in the current study (Table 3.6). These were enteropathogens (Shigella, Rotavirus, Cryptosporidium and ETEC), socio-economic (house type, flush toilet, piped water), duration of current residence, associations with childhood diarrhoea that were not inherently seasonal (age, duration of diarrhoea before admission, duration of vomiting, being breast-fed, weight for height, degree of dehydration) and plasma pH. After adjustment for confounding in the multiple regression analyses, several of these variables lost statistical significance, reflecting confounding associations.

3.6.1.1 Multiple regression analysis for plasma sodium

After adjustment for confounding in the multiple regression analysis, the following variables remained significantly associated with plasma sodium levels; ETEC, EPEC, type of housing, breastfeeding, age and pH.

a) Seasonally distributed independent variables

The patients infected with ETEC and EPEC had on average 5.12 mmol/l and 2.13 mmol/l lower plasma sodium concentrations respectively compared to those without these infections. Both these enteropathogens were more common in summer/autumn, for both absolute numbers and proportions of total stool specimens collected per month (Figures 3.8 and 3.9), and both had summer /autumn peaks similar to those reported previously (Household *et al.*, 1988; Qadri *et al.*, 2000). Because of their seasonal variation in parallel with the fluctuations in plasma sodium levels, these organisms are the most directly related to the seasonal plasma sodium fluctuations, and appear to be

their most likely direct explanation. This is the first report of such a finding. In the previous study in this setting, the seasonal difference in the monthly mean sodium levels of 6.0 mmol/l translated into a more than 12-fold difference in the prevalence of severe hypernatraemia (>160 mmol/l) between summer and winter months (Swingler & Power, 2002). The variation in sodium levels of 5.12 mmol/l and 2.13 mmol/l attributable to ETEC and EPEC infection respectively in the current study suggests that these enteropathogens are of considerable clinical and public health importance. This effect could be mediated by increased sodium losses in stools. Stool volume sodium concentration have been found to be higher in ETEC than in rotavirus infections, providing some support for this hypothesis (Molla *et al.,* 1981).

b) Socio-economic variables

Plasma sodium levels were associated with type of housing. Patients residing in brick houses had on average 2.66 mmol/l higher plasma sodium concentrations than those living in shacks. The association with type of housing is thus of a similar magnitude as EPEC infection, but housing is not inherently seasonal so it would not contribute to seasonal variations unless there were an unmeasured confounding factor. The type of housing may however reflect broader socio-economic status. This positive association of high levels of plasma sodium with higher socio-economic status has been previously reported (Yousuf *et al.*, 1988).

In this study housing could have influenced sodium levels by different pathways, as illustrated in the discussion in Section 3.4.3 of the potential impact of piped water. The availability of piped water and a flush toilet were also associated with sodium levels in the bivariate analysis, but these associations disappeared in the multivariate analysis, suggesting that they are confounders of the association with type of house. It remains unclear whether the type of housing itself or some other unmeasured confounder associated with socio-economic status is a determinant of the plasma sodium

levels, for example, health-seeking behaviour and subsequent treatment practices, as suggested by Yousuf *et al.* (1988). Children living in brick houses presented more frequently in summer, but this association is in the opposite direction to that required to explain seasonal fluctuations in plasma sodium levels.

c) Associations with childhood diarrhoea that were not inherently seasonal

Plasma sodium concentration decreased by 0.29 mmol/l with each one-month increase in the patients' age. Assuming a linear association with plasma sodium, brick housing would have a similar strength of association as an increase of nine months in age, suggesting that the association of sodium levels with age is also of practical importance. This negative association between age and plasma sodium levels has been reported previously (Ahmed & Agusto-Odutola, 1970; Fayad *et al.*, 1992; Samadi *et al.*, 1983) and could be due to the fact that younger children have immature renal function and are unable to deal with a high solute load. There was however no significant association of age with season, so age does not explain the seasonal variation in plasma sodium levels.

Patients who were breast-fed had on average 1.91 mmol/l higher plasma sodium concentration than those not drinking breast milk. The association with breast-feeding is surprising because of the lower plasma sodium content of breast milk compared with formula feeds. However this phenomenon has been reported previously for very young children when they were not exclusively breast-fed but were continually fed with both formula milk and breast milk (Ahmed & Agusto-Odutola, 1970). The many complex associations with breast-feeding, including nutritional and HIV status, make a simple explanation of its relationship with plasma sodium concentrations difficult. The higher prevalence of breastfeeding in winter could explain some of the observed seasonal fluctuations with seasonal association the result of an unknown confounding factor.

of one year in parental education. Assuming a linear association with plasma potassium, the presence of Cryptosporidium would have a similar strength of association as seven or eight years of education, suggesting that the association is less marked. The positive association between parental education and increased potassium could be explained by the fact that a increased parental education is known to be associated with decreased risk of diarrhoea (Ahiadeke, 2000; Mahalanabis *et al.,* 1996) and specific care-giving practices with respect to diarrhoea that were not recorded in the current study (like better hygiene). However, this finding could also reflect broader socio-economic status and be due to other unmeasured confounders associated with that status. There was however no significant association of parental education with season, so parental education does not explain the seasonal variation in plasma potassium levels.

c) Associations with childhood diarrhoea that were not inherently seasonal

Plasma potassium concentrations decreased by 0.02 mmol/l for every additional day that the patient had diarrhoea before admission. The decrease in potassium levels as duration of diarrhoea increases was reported previously by Zaman *et al.* (1985) and could be due to ongoing potassium losses. There was however no significant association of duration of diarrhoea prior to admission with season, so duration of diarrhoea does not explain the seasonal variation in plasma potassium levels.

d) Plasma pH

The association of plasma potassium with pH was expected, as mentioned above in the case of plasma sodium levels.

3.6.1.3 Effect modifiers

Degree of dehydration was found to be an effect modifier of the association

between breast-feeding and sodium (Table 3.10). This association was stronger in patients that were more dehydrated. As with breast-feeding, this association is difficult to explain, particularly because the mechanism of the association itself is not understood. It should be noted that the probability of this finding occurring by chance was 0.01, and that it was the only statistically significant finding among 40 interactions examined. This finding may thus be due to chance and should be regarded with caution.

3.6.1.4 Possible determinants of the parallel seasonal fluctuations of plasma sodium and potassium levels

A striking feature of the seasonal fluctuations of plasma sodium and potassium that was confirmed by this study is the parallel nature of the fluctuations in both these electrolytes. This suggests that the fluctuations have some determinants in common. Of the variables measured in this study, only the enteropathogens appear to explain these fluctuations. Different organisms were significantly associated with plasma sodium and potassium levels - ETEC and EPEC with plasma sodium and Cryptosporidium with plasma potassium. However, ETEC and Cryptosporidium both have a similar seasonal distribution (Figures 3.8 and 3.10), and were both: i) associated with both plasma sodium and potassium in the bivariate analyses and ii) have associations in the same direction (whether significant or not) in the multivariate analyses. It appears that the seasonal fluctuations of plasma sodium and potassium levels are at least partly explained by both ETEC and Cryptosporidium working together, with ETEC having the larger effect on plasma sodium and Cryptosporidium the larger effect on plasma potassium.

It is conceivable that the other variables associated with plasma sodium and potassium levels have had a seasonal effect via confounding factors such as migration, health service utilisation or climatic variation. Residing in a brick house (p=0.010) and being breastfed (p=0.040) were in fact seasonally distributed. The association with brick housing was in the opposite direction

to that required for it to explain the seasonal variation of plasma sodium observed on this study. The higher prevalence of breastfeeding in winter could explain some of the observed seasonal fluctuations, though presumably via an unknown confounding factor. No seasonal distribution was observed for age (p=0.230), parental education (p=0.531) and duration of diarrhoea (p=0.110).

3.6.2 Strengths of the research

The study population was broadly representative of children with dehydrating diarrhoea from urban and peri-urban areas as well as informal settlements in the Cape metropolis. This increased the generalisability of the findings.

The sampling strategy used captured the seasonal pattern of the aetiological factors being assessed, even though small numbers of patients were enrolled in the quieter winter months. Although an interim sampling strategy was used to ensure sufficient numerical representation of stool specimens across seasons, a sensitivity analysis showed that there was no significant difference between the patients admitted and recruited during work hours and those admitted overnight but enrolled the following day (Table 3.13).

Socio-economic and socio-demographic data were collected prospectively, resulting in a greater level of accuracy in the information reported.

Associations with aetiological factors and plasma sodium and potassium levels were determined by multiple regression analysis that adjusted for confounding effects between the factors.

3.6.3 Limitations of the research

Socio-economic status as a single composite variable was very difficult to define (Montgomery *et al.*, 1997). A limited number of factors with

established associations with socio-economic status (Ahiadeke, 2000; Mahalanabis *et al.*, 1996; WHO, 2000) were chosen since they would have partly mediated an association with diarrhoea. Thus many other unrecognised factors could have been missed and these could have been responsible for some of the findings reported in the current study (such as the association between type of housing and plasma sodium, and that of paternal education and plasma potassium).

The principal investigator was not blind to the plasma sodium and potassium results when administering the questionnaires. As a prerequisite for the study in Chapter Four, the principal investigator examined the patient's folder and concealed any electrolyte results before examination of the patient by the admitting medical officer. The patient's folder was thus examined immediately after the caregiver agreed to participate in the study and before the administration of the questionnaires. This was necessary to ensure that the medical officers participating in the study reported in Chapter Four were blinded to the measured outcomes as the medical officers assessed the clinical signs, not the principle investigator. This was unavoidable as overlapping data collection for two different studies was occurring simultaneously and resources were insufficient for an additional investigator.

Lack of investigator blinding could potentially have introduced information bias particularly in the collection of more subjective data. However, no seasonal associations were found with these more subjective variables, whereas the observed significant associations were found with more objective micriobiological investigations which were performed by laboratory staff that were blinded to the electrolyte results.

3.6.4 Implications for practice/public health responses

The apparent seasonal variation of plasma electrolyte levels having a major impact on the prevalence of severe electrolyte disturbances has been

confirmed in this study, using different prospective methods of sampling. These fluctuations thus need to be taken seriously.

Associations of electrolyte levels with the enteropathogens ETEC, EPEC and Cryptosporidium were identified and these explained a large proportion of the seasonal fluctuations observed in electrolyte levels that were large enough to be of clinical and public health importance. This study has however not identified specific focussed interventions to immediately and directly prevent electrolyte disturbances attributable to seasonal fluctuations in mean plasma sodium and potassium levels. Further evidence around the determinants of the microbial infections themselves is needed before specific action can be formulated.

Socio-economic factors such as housing and parental education were identified as determinants of electrolyte levels, if not their seasonal fluctuations. Although electrolyte disturbances themselves do not appear to justify the considerable resources required to improve housing and education, these findings add a further reason to the many already existing for the improvement of socio-economic status, including housing and education.

This study has highlighted the importance of interventions to improve parental education and socio-economic status, particularly housing, since these factors were shown to impact on the health of the child. They do not, however, suggest additional targeted interventions to prevent electrolyte disturbances in childhood diarrhoea.

3.6.5 Implications for future research

The most important and potentially most preventable determinants identified for the first time in this study are also in the area in which the most important gaps in knowledge still exist. Following the identification of the specific microbes, information is required on the determinants of the microbial

infections themselves. Further investigation of associations of nutritional and environmental factors with these enteropathogens, particularly in the context of childhood diarrhoea, would provide insight into prevention of the electrolyte disturbances.

As a first step, an analysis of the existing database compiled for the current research to identify nutritional and environmental determinants of both ETEC and Cryptosporidium is currently under way.

3.7 Conclusions

Seasonal fluctuations in plasma sodium and potassium levels reported previously have been confirmed by the current study.

Plasma sodium levels were negatively associated with age, ETEC infection and EPEC infection, and positively associated with being breast-fed and living in a brick house. The clinically meaningful seasonal fluctuations of plasma sodium levels are at least partly determined by ETEC and EPEC. The negative association between plasma sodium levels and ETEC and EPEC infection is a new contribution to the present body of research.

Plasma potassium levels were positively associated with increased parental education, and negatively associated with the numbers of days with diarrhoea before admission and Cryptosporidium infection. As with plasma sodium levels, the clinically meaningful seasonal fluctuations in plasma potassium levels are at least partly determined by infection with Cryptosporidium. The negative association between plasma potassium levels and Cryptosporidium infection is also a new contribution to the present body of research.

The striking *parallel* seasonal fluctuations of plasma sodium and potassium levels are at least partly explained by both ETEC and Cryptosporidium working together, with ETEC having the larger effect on plasma sodium levels and Cryptosporidium on plasma potassium levels.

Identification of the specific determinants of ETEC and Cryptosporidium infection could help formulate a more specific approach to preventing disturbances in plasma sodium and potassium levels.

These findings provide further support for existing interventions to improve parental education and socio-economic status (including housing). They do not, however, suggest additional targeted interventions to prevent the seasonal disturbances in plasma sodium and potassium in diarrhoea.

CHAPTER FOUR: UTILITY OF CLINICAL SIGNS IN THE DIAGNOSIS OF PLASMA SODIUM AND POTASSIUM ABNORMALITIES IN CHILDHOOD DIARRHOEA

4.1 Background

Clinical examination (history and physical examination of the patient) can be a powerful tool for establishing diagnosis and prognosis, and guiding treatment of the presenting patient. However, the usefulness of such an examination is dependent on the accuracy of clinical features used to identify possible target conditions in the patient (Sackett *et al.*, 1991:19).

Several clinical signs of hypernatraemia, hyponatraemia and hypokalaemia are generally accepted (Chhabra *et al.*, 1995; Rudzinski *et al.*, 1996:342, 346). These clinical signs of plasma sodium and potassium disturbances appear to have been based on case series of children with the electrolyte disturbances. Such case series are of limited usefulness, as they do not include patients without the abnormalities and provide no information on whether a specific clinical feature is helpful in discriminating those children with the disturbance from those without it. Signs reported to be associated with abnormal plasma sodium levels are irritability (Kuzemko, 1969; Rudzinski *et al.*, 1996:342), seizures (Rudzinski *et al.*, 1996:342), depressed level of consciousness (Kuzemko, 1969; Rudzinski *et al.*, 1996:342), a wooden feel to the skin (Rudzinski *et al.*, 1996:342), weakness (Barkin, 1997, cited in Johns Hopkins, 2002:244) and increased biceps and knee reflexes (Johns Hopkins, 2002:244). Signs reported to be associated with abnormally low potassium levels are hypotonia, physical weakness (Barkin, 1997, cited in Johns Hopkins, 2002:241; Chhabra *et al.*, 1995; Rudzinski *et al.*, 1996:346), ileus (Chhabra *et al.*, 1995; Rudzinski *et al.*, 1996:346) and abdominal distension (Chhabra *et al.*, 1995).

The utility of clinical signs in the diagnosis of a target condition also depends on the ability of the clinical feature to distinguish children with the disorder of

interest from those without the disorder in a clinical context where other conditions may produce similar signs. An example of this, hypotonia occurs in hypokalaemia (Chhabra *et al.*, 1995) and a depressed level of consciousness in hypernatraemia (Rudzinski *et al.*, 1996:342); however, both are important features of shock due to dehydration (American Academy of Pediatrics, 1994:2-6) and can appear together with, or independently of, electrolyte disturbances. Hypotonia occurring in dehydration will therefore not necessarily indicate hypokalaemia, nor will a depressed level of consciousness necessarily indicate hypernatraemia. Equally, because not all children with hypokalaemia are hypotonic, the absence of this sign does not necessarily exclude hypokalaemia.

False-negative (see glossary) signs can lead to important conditions being missed and not receiving attention, while false-positive (see glossary) signs may result in parental anxiety and exposure to unnecessary and potentially harmful further investigations or treatment.

4.1.1 Review of the literature on diagnostic accuracy of clinical signs for plasma sodium and potassium abnormalities in children less than 2 years old with diarrhoea

4.1.1.1 Identification of relevant studies

A PubMed search (search strategy reported in Appendix 4.1) was performed for the period 1966 to May 2005. One-hundred and eighty-six studies were identified in the search. The abstracts of these studies were screened by the principal investigator to identify those that met the criteria of reporting on i) the diagnostic accuracy ii) of clinical features to detect iii) plasma electrolyte disturbances iv) in children v) with diarrhoea. Sixty-six studies were deemed possibly relevant and full reports were obtained, to enable fuller assessment. The reference lists of identified studies were also screened for potentially relevant reports.

4.1.1.2 Results of literature review

After reading full reports of articles that were potentially eligible for inclusion, no studies were found that were specifically designed to assess the diagnostic accuracy of clinical signs of electrolyte disturbances in children with dehydrating diarrhoea. However, three studies were identified that related to the research question and these will be discussed.

a) Reliability of clinical signs in diarrhoea and other childhood illnesses

One study was identified that reported on the reliability of clinical signs in sick children in Tanzania but no reference standards were used Kahigwa *et al.*, 2002). They assessed inter-observer variability of clinical signs used for the diagnoses of malaria, pneumonia, malnutrition, anaemia and diarrhoea in 327 sick children admitted to a hospital in Tanzania. Clinical officers performed the assessment of signs in any child between 4 months and 6 years of age being admitted to their paediatric ward. The authors concluded that signs were more likely to be agreed upon by clinicians if they involved inspection rather than auscultation. Clinicians showed only fair agreement (Kappa score [see glossary] 0.21-0.40) in the detection of neck stiffness and chest in-drawing, and slight agreement in the detection of dehydration (Kappa score 0.2). Objective assessment of neurological signs was less reliable in infants than in older children, and there were difficulties surrounding the diagnosis of impaired consciousness in young children (*ibid*). The validity of the signs in detecting a target condition was not assessed.

b) Clinical signs of hypernatraemia in a developing country

Hill *et al.* (1981) performed a comparative study that attempted to define clinical signs that were useful in distinguishing between hypernatraemic and non-hypernatraemic children by determining if there was a significant difference in the groups with and without the signs. No formal assessment of

the diagnostic accuracy or reliability of clinical signs was performed, but measures of diagnostic accuracy could be calculated from data extracted from the report (Table 4.1).

One hundred and ninety-seven patients admitted to the drip room (now the Rehydration Unit) at Red Cross Children's Hospital were enrolled into the study. All patients with serum sodium levels >150 mmol/l, regardless of time of presentation, were enrolled into the study. This group was compared to a consecutive sample of patients with normal serum sodium levels enrolled during specified work hours during the week. One hundred and forty-seven of the patients (74.6%) were hypernatraemic (*ibid*).

Contingency tables of data used to calculate measures of diagnostic accuracy are presented in Appendix 4.2. Jitteriness was 100% specific for hypernatraemic patients, with no false-negatives and a positive predictive value of 100%. It was, however, not sensitive (14%), with a negative predictive value of 35%. Similarly, coma/convulsions/drowsy were very specific (96%), with high positive predictive values (95%), but not very sensitive (31%), with low negative predictive values (35%). Coma/convulsions/drowsy had a clinically meaningful association with hypernatraemia.

Some aspects of the study design need to be considered when interpreting the findings, as these could have contributed to an exaggerated estimate of diagnostic accuracy. These are the following: i) clinical signs were assessed with the knowledge of the serum sodium levels (the reference standard) thus introducing potential test review bias (see glossary); ii) different sampling techniques were used to enrol hypernatraemic and non-hypernatraemic patients thus introducing potential selection and spectrum bias (see glossary); and iii) only one clinician performed all the clinical assessments, and not a representative range of clinicians, limiting the applicability of the findings to actual clinical practice.

Table 4.1 Measures of diagnostic accuracy (for binary responses) calculated from extracted data (Hill *et al.*, 1981)

	Jittery	Coma/convulsions/drowsy
†Sensitivity (%)	14	31
95% CI	7.52 to 20.8	23.2 to 39.0
†Specificity (%)	100	96
95% CI	92.6 to 100	86.3 to 99.5
†Positive predictive value (%)	100	95
95% CI	78.2 to 100	84.0 to 99.4
†Negative predictive value (%)	35	35
95% CI	26.6 to 42.4	26.6 to 42.4

*Unable to calculate as the denominator was zero and the likelihood ratios approached infinity.

†See glossary for definitions.

Even though the prevalence of hypernatraemia was high, the sample was small, therefore some of the estimates lacked precision (broad 95% confidence intervals), implying that the findings could be due to chance.

c) Clinical signs of hypernatraemia in a developed country

Another study (Tjon A Ten, 1999) was identified that reported on the frequency and management of electrolyte disturbances in children with acute diarrhoea admitted to their hospital between January 1992 and December 1999. Unclear reporting of the study methods made appraisal of the validity of the findings difficult. The report implied that a consecutive sampling technique was used for enrolment into the study. Two hundred and sixty-five children were enrolled into the study; however, serum sodium levels were only available for 192 of these patients (*ibid*). As part of the study, data were presented on how often children that were hypernatraemic and those that were normal presented with clinical dehydration. These data were extracted and measures of diagnostic accuracy were calculated (Table 4.2), making the considerable assumption that those patients with missing data for serum sodium levels all had normal serum sodium levels.

Table 4.2 Measures of diagnostic accuracy (for binary responses) calculated from extracted data (Tjon A Ten, 1999)

	Clinically dehydrated
†Sensitivity (%)	7
95% CI	2.23 to 15.1
†Specificity (%)	98
95% CI	95.5 to 99.7
†Positive predictive value (%)	63
95% CI	24.5 to 91.5
†Negative predictive value (%)	73
95% CI	67.7 to 78.6

†See glossary for definitions.

Eight (3%) of the patients were hypernatraemic. Contingency tables for data used to calculate measures of diagnostic accuracy are reported in Appendix 4.2. Clinical dehydration was very specific (98%) but not sensitive (7%). Clinical dehydration had a limited clinically meaningful association with hypernatraemia. Estimates of diagnostic accuracy lacked precision (broad 95% CI) and could be due to chance.

The above study was performed in Holland where dehydrating diarrhoea is less common, and children are expected to be generally healthier and present with milder dehydration and better nutritional status. Only 74 (27.9%) of the 265 children were in fact assessed as being dehydrated.

4.1.1.3 Summary of the literature review

One study was found that reported on inter-observer agreement for a number of clinical signs used to identify a broad spectrum of conditions, including diarrhoea. Agreement was better when signs involved inspection than when they involved auscultation, there was slight agreement in the detection of dehydration (Kappa score 0.2), and objective assessment of neurological signs and impaired consciousness were less reliable and difficult in infants and younger children (Kahigwa *et al.*, 2002).

Two other studies designed and performed for other primary objectives reported data that could be re-analysed to assess diagnostic accuracy of a limited number of signs. One of these studies (Hill *et al.*, 1981) suggested potentially useful accuracy of jitteriness and disturbances of level of consciousness in detecting hypernatraemia, but the findings are susceptible to bias because of several aspects of the study design. The second study (Tjon A Ten, 1999) enabled only a very approximate estimate of dehydration as a sign of hypernatraemia in a sample of children not representative of those in low- and middle-income countries where dehydrating diarrhoea is more prevalent.

4.1.2 Review of the literature on diagnostic accuracy of clinical signs for plasma sodium and potassium abnormalities in children less than 2 years old in conditions other than diarrhoea

4.1.2.1 Identification of relevant studies

A broad and sensitive PubMed search was performed, using the "Clinical Queries" strategy for the period 1966 to December 2005, for clinical signs of electrolyte disturbances in children under 2 years of age. It identified 152 studies for hypokalaemia, 120 studies for hypernatraemia and 268 studies for hyponatraemia (search strategy reported in Appendix 4.1). The abstracts of these studies were screened by the principal investigator to identify those that met the criteria of reporting on i) the diagnostic accuracy ii) of clinical features to detect iii) plasma electrolyte disturbances iv) in children less than 2 years old. Three studies were deemed possibly relevant and full reports were obtained, to enable fuller assessment. The reference lists of identified studies were also screened for potentially relevant reports.

4.1.2.2 Results of literature review

None of the studies met the inclusion criteria reported in section 4.1.2.1.

There are thus no reliable data, in children, on the diagnostic accuracy of clinical tests for important electrolyte disturbances. This is particularly important in children with dehydrating diarrhoea as these children are usually managed in settings where facilities for laboratory diagnosis of electrolyte disorders are not easily available, if they are at all. This study will investigate the diagnostic accuracy of clinical features in detecting plasma sodium and potassium disturbances in childhood diarrhoea.

4.2 Aims of study

The aim of this study was to assess the diagnostic accuracy and reliability of clinical signs previously reported to be associated with electrolyte disturbances in children admitted to a diarrhoea Rehydration Unit.

4.3 Objectives

a) To determine the likelihood ratios for the presence or absence of clinical signs, or a combination of clinical signs, for:
   - hypernatraemia,
   - severe hypernatraemia,
   - hyponatraemia,
   - hypokalaemia,
   - severe hypokalaemia.

b) To determine the sensitivity, specificity and predictive values for the clinical signs with a binary response.

c) To measure inter-observer variation (reliability) in assessing these clinical signs.

4.4 Methods

4.4.1 Inclusion and exclusion criteria

All patients with the primary diagnosis of diarrhoea between 6 weeks and 2 years of age admitted to the Rehydration Unit at Red Cross Children's Hospital, Cape Town, during work hours were enrolled into the study after written informed consent was obtained from the caregiver. Patients with any neurological disorders, for example, cerebral palsy or developmental delay were excluded.

4.4.2 Sampling

A consecutive sampling technique was used and is described in detail in section 2.3. Table 4.3 reports the number of enrolments targeted per month.

Table 4.3 Targeted enrolment per month

Month	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Total
Target	75	90	114	92	65	41	33	30	32	36	40	52	700

4.4.3 Data collection

All medical officers working in the Rehydration Unit were provided with an information sheet on the study at the beginning of their two-month rotation in the Unit (Appendix 4.3). Patients referred to the Rehydration Unit were enrolled into the study on arrival, before they were examined by the admitting medical officer on duty. During the admission examination this medical officer recorded on the data capture sheet (Appendix 4.4) attached to the patient's folder the clinical findings detailed in section 4.4.3.2 below. The medical officers were typically either doctors performing statutory community service immediately post internship, or other recently qualified medical practitioners.

4.4.3.1 Reference standard (target conditions studied)

Measured plasma sodium and potassium concentrations were used as the reference standards. Plasma potassium and plasma sodium concentrations were measured by the hospital's routine clinical laboratory using the direct ion-electrode method.

Electrolyte disturbances were defined as:

Hypernatraemia	Plasma sodium above 150 mmol/l
Severe hypernatraemia	Plasma sodium above 158 mmol/l

Hyponatraemia	Plasma sodium below 135 mmol/l
Hypokalaemia	Plasma potassium below 3.5 mmol/l
Severe hypokalaemia	Plasma potassium below 2.5 mmol/l

Results were extracted from routine laboratory records by the principal investigator and recorded on the laboratory results data extraction form (see Appendix 3.2).

4.4.3.2 Clinical signs studied

a) The following clinical signs were assessed for plasma sodium disturbances. The levels of response for each sign are reported in the outer brackets.

- *Irritability* (reported by the caregiver to have occurred for the current episode of diarrhoea) (crying consolably or inconsolably/normal),
- *Seizures* (reported by the caregiver to have occurred 24 hours prior to admission) (yes/no),
- *Level of consciousness* (Glasgow Coma Score [see Table 4.4]) (<8 /8-12/ >12),
- Weakness:
    - *Resists procedures* (for example, when taking blood) (yes/maybe/no),
    - *Kicks away* (complete leg extension from flexion) (yes/maybe/no),
    - *Pushes away* (gravity overcome) (yes/maybe/no),
    - *Lifts head from bed* (prone, ≥ 6 weeks) (yes/maybe/no),
    - *Sits unsupported* (≥ 7 months) (yes/maybe/no),
    - *Rolls over* (≥ 9months) (yes/maybe/no),
    - *Stands* (≥ 12months) (yes/maybe/no),
- *Wooden feel to skin* (yes/maybe/no),
- *Tendon reflexes,* namely biceps and knee (reduced/normal/brisk),

- *Adequacy of peripheral perfusion* (poor/fair/good),
- *Degree of dehydration* (10% / 5% /potentially dehydrated/good).

b) The following clinical signs were assessed for potassium disturbances. The levels of response for each sign are reported in the outer brackets.

- *Level of consciousness* (Glasgow Coma Score [see Table 4.4]) (<8/8-12/ >12),
- Hypotonia:
  - *Lies in frog's leg position* (yes/maybe/no),
  - *Marked head lag on pulling to sit* (if >3 months) (yes/maybe/no),
  - *Marked truncal slump on sitting* (if > 7 months), (yes/maybe/no),
- Weakness:
  - *Resists procedures* (for example, when taking blood) (yes/maybe/no),
  - *Kicks away* (complete leg extension from flexion) (yes/maybe/no),
  - *Pushes away* (gravity overcome) (yes/maybe/no),
  - *Lifts head from bed* (prone, ≥ 6 weeks) (yes/maybe/no),
  - *Sits unsupported* (≥ 7 months) (yes/maybe/no),
  - *Rolls over* (≥ 9months) (yes/maybe/no),
  - *Stands* (≥ 12months) (yes/maybe/no),
- *Ileus* (yes/maybe/no),
- *Abdominal distension* (in an non-obese child, elevation of the abdominal wall higher than the chest wall when viewed from the side) (yes/maybe/no),
- *Adequacy of peripheral perfusion* (poor/fair/good),
- *Degree of dehydration* (≥10% / 5% /potentially dehydrated/good).

Provision was made on the data capture sheet for clinical signs not assessed because they were: not applicable (age-dependent); difficult to assess (not elicited); or not reported (not done).

Although not mentioned in the initial protocol, data on the adequacy of peripheral perfusion and degree of dehydration were prospectively collected and included in the analysis because they appeared to be potentially important signs for the operational management of electrolyte disturbances, if sufficiently accurate.

4.4.3.3 Rationale for category cut-off points

All categories of response for clinical signs and levels of plasma sodium and potassium used to define the different electrolyte disturbances were chosen prior to commencement of the research.

Hypernatraemia has a well-recognised cut-off level of >150 mmol/l. Cut-offs for severe hypernatraemia (158 mmol/l) and severe hypokalaemia (<2.5 mmol/l) were chosen because concentrations beyond these levels have been reported sometimes to be life-threatening (Adelman & Solhung, 1996:218; Travis, 1996:1331). The levels chosen for hyponatraemia (<135 mmol/l) and hypokalaemia (<3.5 mmol/l) were the laboratory cut-offs at Red Cross Children's Hospital.

Operational definitions were provided for clinical signs, but clear-cut offs between normal and abnormal were often difficult to define because of the clinical judgement required in the context of the smooth continuum between normal and abnormal. To accommodate this ambiguity an equivocal category was included, in addition to "yes" and "no", and was analysed with the use of likelihood ratios and weighted Kappa (section 4.4.4 and 4.4.5).

The Glasgow Coma Score is made up of the components reported in Table

4.4. This score is widely used to describe the level of consciousness and cut-offs were those being used in current clinical practice at Red Cross Children's Hospital.

Table 4.4 Description of Glasgow Coma Score as used at Red Cross Children's Hospital

Component of Score	Level of response	Scoring for each level
Eyes opening	Spontaneously	4
	To speech	3
	To pain	2
	No response	1
Best motor response	Obeys/normal spontaneous movement	6
	Localises pain	5
	Flexion withdrawal	4
	Flexor posturing	3
	Extensor posturing	2
	No response	1
Best verbal response	Coos and babbles	5
	Irritable/cries	4
	Cries in response to pain	3
	Grunts	2
	No response	1

Swingler, 2004:481.

4.4.3.4 Blinding

Patients' folders were examined by the principal investigator prior to clinical examination of the patient by the admitting medical officer. Any electrolyte results already available in the folder were concealed with a removable self-adhesive label to ensure that the medical officer made the clinical assessment before obtaining access to the electrolyte results. Blinding was not tested because it was judged not to be possible.

4.4.4 Measures of diagnostic accuracy

Likelihood ratios (LRs) were used as the primary measure of diagnostic accuracy. An LR is the ratio of the likelihood that a given test result is expected in a patient with the target disorder, compared to the likelihood that that same result is expected in a patient without the target disorder (Jaeschke *et al.*, 2002:198).

These ratios incorporate both sensitivity (the proportion of patients with the target disorder with a positive test) and specificity (the proportion of patients without the target disorder with a negative test) to describe the change in odds favouring the presence of the target disorder given a particular test result (Jaeschke *et al.*, 2002:203). LRs are more useful to clinicians than sensitivity and specificity since they reflect the change in the odds of the condition due to the test result in an individual patient before the disease status of the patient is known (Simel *et al.*, 1991). Other advantages that LRs have over sensitivity and specificity are that they can be calculated for several levels of the sign or test (for example, they can include an equivocal category) and they can be used to combine the results of multiple diagnostic tests (Sackett *et al.*, 1991:120, 131).

LRs are also advantageous over predictive values (see glossary) since they are not dependent on prevalence of the target condition (Altman, 1991:411) like predictive values.

LRs of 1 indicate no association between the target disorder and the sign or test; LRs greater than 1 indicate that the test result increases the probability that the target disorder is present (the higher the LR, the greater the increase in probability), while LRs less than 1 indicate that the test result decreases the probability of the target disorder (the smaller the LR, the greater the decrease in probability) (Jaeschke et al., 2002:199). Table 4.5 suggests a broad interpretation of the meaning of LRs of different sizes.

Table 4.5 Suggested interpretation of likelihood ratios

	Likelihood ratios	
	Positive test	**Negative test**
No use at all	1	1
Alters probability to a small (and rarely important) degree of the target condition	1 - 2	0.5 - 1
Generates small (but sometimes important) changes in probability of the target condition	2 - 5	0.5 - 0.2
Generates moderate change from pre-test to post-test probability (see glossary) of the target condition	5 - 10	0.1 - 0.2
Generates large and often conclusive change from pre-test probability to post-test probability of the target condition	>10	0.1

Jaeschke *et al.*, 2002:199.

4.4.5 Reliability of clinical signs

Inter-observer variation was assessed by two medical officers eliciting the same clinical signs on the same patient, within 10 minutes of each other, without knowledge of electrolyte results or their colleague's assessment. This reliability study was performed between October 2003 and March 2004, using convenience samples of children in the Rehydration Unit at times convenient to the medical officers who were recruited for this study. Three medical officers participated in different pairs. Two of these medical officers had participated in the clinical examination of patients recruited to the study of diagnostic accuracy, and the third was a clinical researcher who had recently also worked as a medical officer in the Rehydration Unit.

The proportion of potential agreement beyond chance between two medical officers was determined using the weighted Kappa score. The advantage of using the weighted Kappa score rather that the Kappa score is that it makes provision for the different levels of response and weights the degree of disagreement. This means that greater credit is given for minor disagreements than wide disagreements (Altman, 1991:406; Sackett *et al.*,

1991:30, 55). The weighted Kappa score was calculated for each clinical sign to measure agreement between the medical officers.

The following guide has been published for the interpretation of weighted Kappa scores using the following qualitative categories (Sackett *et al.*, 1991:30):

0 = no agreement better than chance,
0 – 0.2 = slight agreement,
0.2 – 0.4 = fair agreement,
0.4 – 0.6 = moderate agreement,
0.6 – 0.8 = substantial agreement,
0.8 – 1.0 = almost perfect agreement.
Negative values indicate worse than chance agreement.

4.4.6 Analysis

Methods of estimation rather than hypothesis testing were used as recommended by Standards for Reporting of Diagnostic Accuracy (Bossuyt *et al.*, 2003). LRs for the presence and absence of clinical signs, with 95% confidence intervals, were calculated (Simel *et al.*, 1991) for each clinical sign for each outcome. Each sign (except history of seizures and irritability) was assessed using more than two levels of response (Appendix 4.4). A decision was made against re-categorising multi-level responses to binary responses in order to calculate sensitivity, specificity and predictive values because important information on definite versus equivocal signs would have been lost (Jaeschke *et al.*, 2002:206).

Logistic regression analysis was planned using clinical signs that showed a clinically meaningful (LR >5), statistically significant association with plasma sodium or potassium disturbances to develop predictive models for the different target conditions.

Receiver operating characteristic curves (see glossary) were planned for the predictive models determined by logistic regression analysis for the different target conditions to assess the sensitivity and specificity of different numbers of signs from the same model.

Sample size calculations for studies of diagnostic accuracy can be guided by estimating a meaningful confidence interval around the desired LR and then using the confidence interval to estimate sample size for the diagnostic test (Simel *et al.*, 1991). The largest sample size was needed for the study of severe hypernatraemia because it was expected to have had the lowest expected prevalence (2.7%). A sample of 700 children would have provided the following approximate 95% confidence intervals for the specified LRs (Table 4.6):

Table 4.6 Expected 95% CI for different estimated likelihood ratios, given a sample of 700 and a prevalence of severe hypernatraemia of 2.7%

Likelihood ratios			
Positive test	**95%CI**	**Negative test**	**95%CI**
1.0	0.65 to 1.50	1.00	0.65 to 1.50
3.5	2.70 to 4.60	0.29	0.13 to 0.61
7.0	5.40 to 9.00	0.14	0.05 to 0.44
10.0	7.70 to 13.00	0.10	0.03 to 0.37

These confidence limits appeared to adequately differentiate different ranges of diagnostic accuracy, except for LRs below 0.20 for negative signs for severe hypernatraemia. Estimates of accuracy below 0.20 would thus indicate useful diagnostic accuracy, but with insufficient precision to determine the degree of usefulness. More useful differentiation between these ranges of diagnostic accuracy for severe hypernatraemia would have required at least twice as many cases.

The precision of estimates of target disorders of higher prevalence, such as severe hypokalaemia, were all higher than for severe hypernatraemia.

Data were managed in the Access 2000 program (Microsoft Corporation, 1992-2001) and analysed in the Excel 2000 program (Microsoft Corporation, 1985-2001).

4.5 Results

A total of 2270 patients were admitted to the Rehydration Unit from 1 April 2002 to 31 March 2003 (data from unpublished routine hospital records). Four-hundred and seventy-six patients were enrolled into the study over a closely related one-year period (15 April 2002 - 14 April 2003). Of these, 475 (99.8%) were included in the final analysis for plasma sodium and 471 (98.9%) for plasma potassium (Figure 4.1). Two hundred and fifty-seven patients (54.1%) had normal plasma sodium levels (135-150 mmol/l), 187 (39.4%) were hyponatraemic, 31 (6.5%) hypernatraemic and 15 (3.2%) severely hypernatraemic. Two hundred and thirty-five patients (49.9%) had normal potassium levels (3.5-5.3 mmol/l), 236 (50.1%) were hypokalaemic and 89 (18.9%) severely hypokalaemic (Figure 4.2).

Figure 4.1 Profile of enrolment – diagnostic accuracy of clinical signs

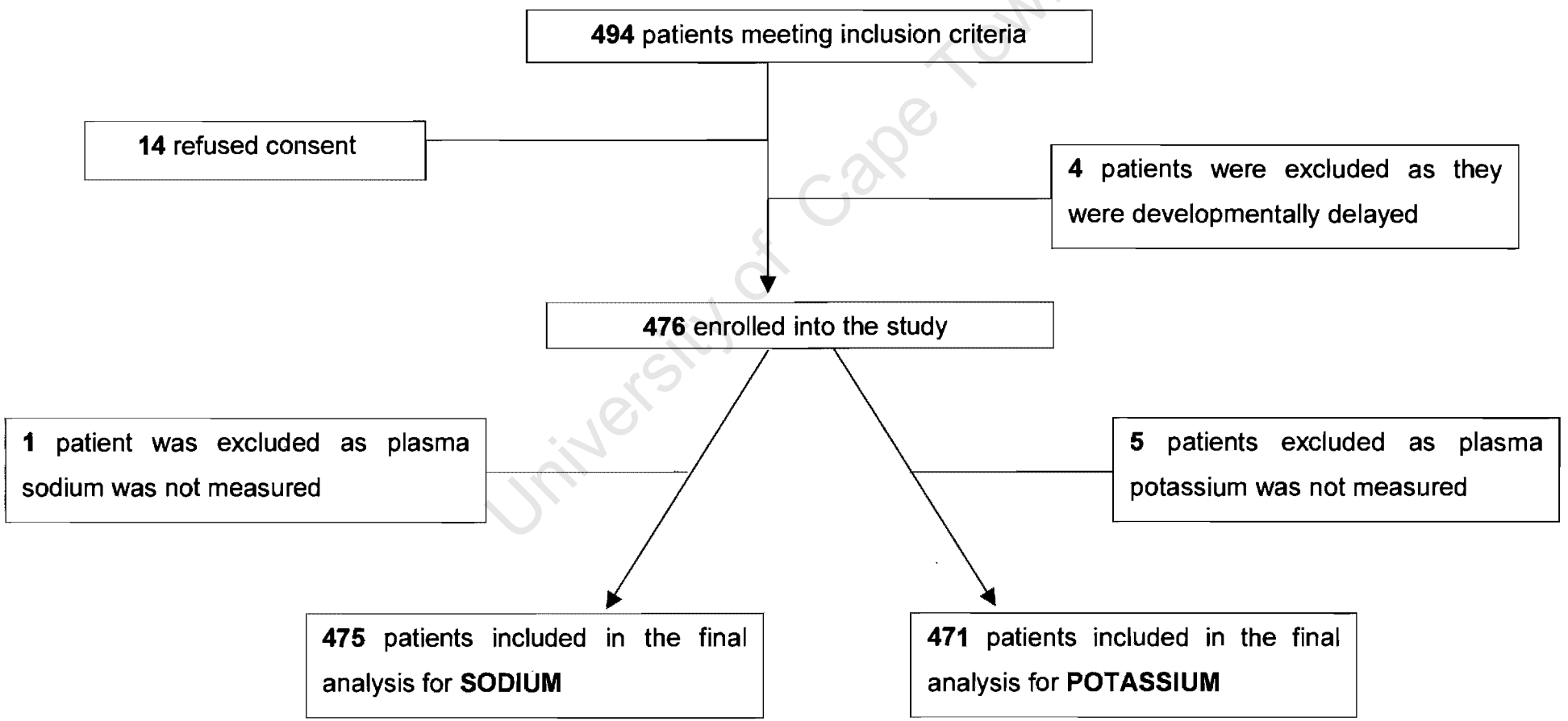
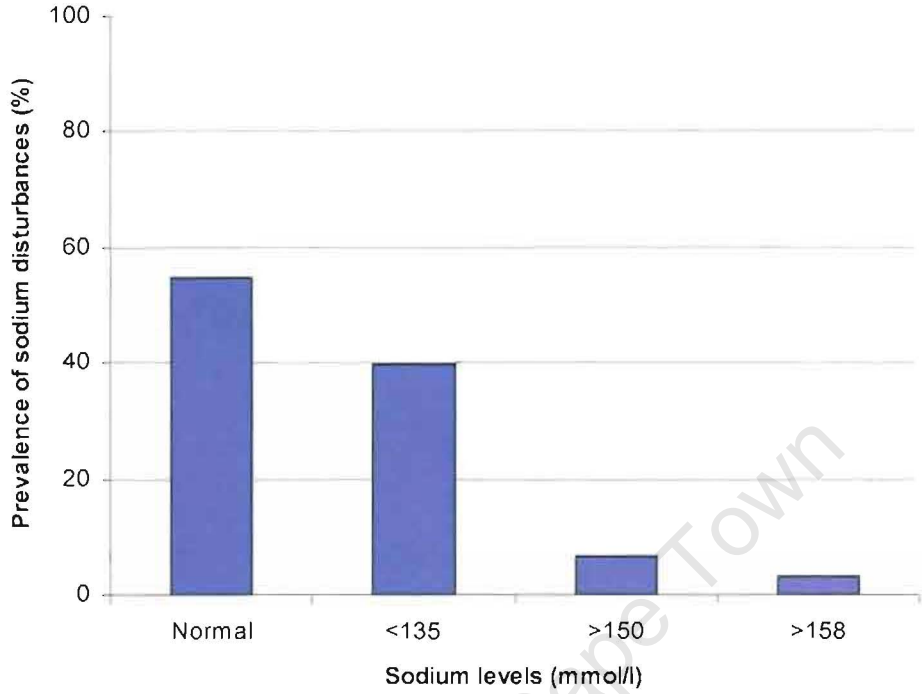
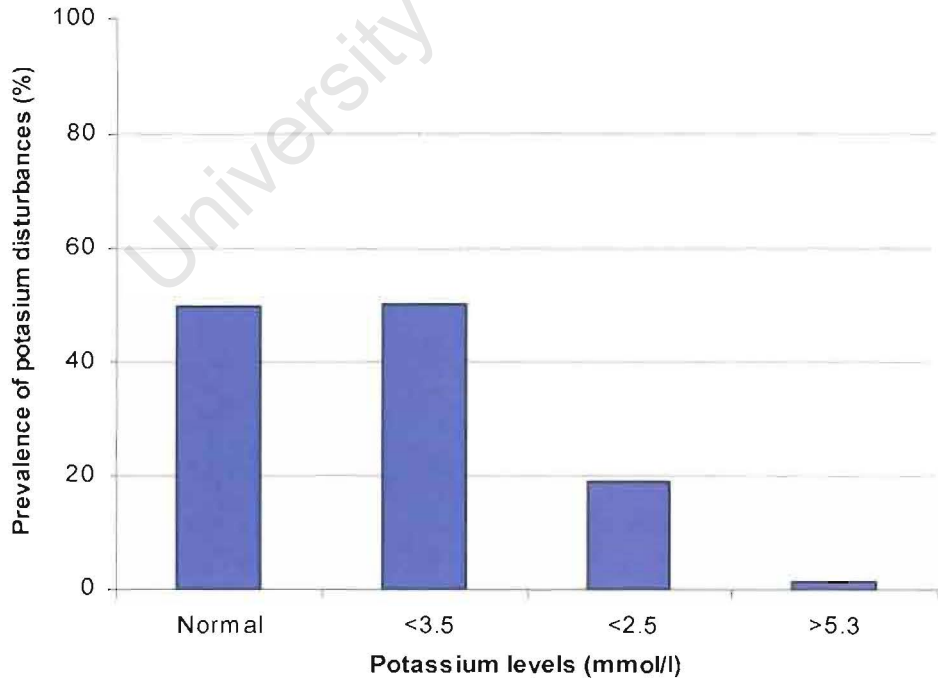


Figure 4.2 Prevalence of sodium (n=475) and potassium disturbances (n=471)





4.5.1 Characteristics of the patients

The median age of patients was 16 months (inter-quartile range 9-21 months). One hundred and ninety-three patients (40.0%) presented with some *co-morbidity. The male to female ratio was 1:1.2. Other characteristics of the patients are listed in Table 4.7.

Table 4.7 Characteristics of patients included in the analysis (N=476)

Nutrition n (%)	Hydration n (%)	Peripheral perfusion n (%)	Gender n (%)
Marasmus/Kwashiorkor	≥ 10% dehydrated	Poor	Males
1 (0.2)	68 (14.3)	43 (9.0)	257 (54.0)
Kwashiorkor	5% dehydrated	Fair	Females
8 (1.7)	227 (47.7)	175 (36.8)	219 (46.0)
Marasmus	Potentially dehydrated	Good	
43 (9.0)	129 (27.1)	246 (51.7)	
Under-weight for age	Good hydration		
134 (28.2)	46 (9.7)		
Normal			
227 (47.7)			

Missing data: *Co-morbidity 154 (32.4%), nutrition (63 [13.2%]), hydration (6 [1.3%]), peripheral perfusion (12 [2.5%]).

4.5.2 Elicitation of clinical signs

Fifty-seven different medical officers and one experienced paediatrician (39 assessments, 8.2%) performed the clinical assessments for this study. Tables 4.8 and 4.9 reports the percentage of observations for clinical signs not elicited and not done. Medical officers experienced difficulty in the assessment of the following signs: sits, rolls over, stands, truncal slump and tendon reflexes.

Table 4.8 Missing data for clinical signs in the analysis of sodium disturbances

Signs for sodium	For the study of diagnostic accuracy						For the study of reliability	
	Missing data (n)	% of 475	Not elicited (n)	% of 475	Not done (n)	% of 475	Not elicited	% of 50
History of irritability	123	25.89	0	0	123	25.89	-	-
History of seizures	4	0.84	0	0	4	0.84	-	-
Level of consciousness	3	0.64	0	0	3	0.64	0	0
Resists procedures	45	9.47	37	7.79	8	1.68	21	42
Kicks away	5	1.05	2	0.42	3	0.63	0	0
Pushes away	5	1.05	1	0.21	4	0.84	0	0
Lifts head	6	1.26	3	0.63	3	0.63	0	0
Wooden feel to skin	3	0.63	0	0.00	3	0.63	0	0
Biceps, tendon reflexes	19	4.00	9	1.89	10	2.11	1	2
Knee, tendon reflexes	17	3.58	7	1.47	10	2.11	1	2
Peripheral perfusion (*N=528*)	13	*2.46	0	0	13	*2.46	-	-
Degree of dehydration (*N=528*)	6	*1.14	0	0	6	*1.14	-	-
◆*Sits (N=302)*	4	*1.32	4	*1.32	0	0	12	24
◆*Rolls (N=252)*	20	*7.94	12	*4.76	8	*3.17	20	40
◆*Stands (N=184)*	4	*2.17	3	*1.63	1	*0.54	20	40

◆Age-dependent variables. *Percentage calculated according to *N* in brackets.

Table 4.9 Missing data for clinical signs in the analysis of potassium disturbances

Signs for potassium	For the study of diagnostic accuracy						For the study of reliability	
	Missing data (n)	% of 471	Not elicited (n)	% of 471	Not done (n)	% of 471	Not elicited	% of 50
Level of consciousness	3	0.64	0	0.00	3	0.64	0	0
Lies in a frog legs position	6	1.27	1	0.21	5	1.06	0	0
Resists procedures	44	9.34	37	7.86	7	1.49	21	42
Kicks away	5	1.06	2	0.42	3	0.64	0	0
Pushes away	5	1.06	1	0.21	4	0.85	0	0
Lifts head	6	1.27	3	0.64	3	0.64	0	0
Ileus	4	0.85	1	0.21	3	0.64	0	0
Abdominal distension	1	0.2	0	0	1	0.2	0	0
Peripheral perfusion (*N=525*)	13	*2.48	0	0	13	*2.48	-	-
Degree of dehydration (*N=525*)	6	*1.14	0	0	6	*1.14	-	-
◆*Sits (N=299)*	4	*1.34	4	*1.34	0	0	12	24
◆*Rolls (N=251)*	20	*7.97	12	*4.78	8	*3.19	20	40
◆*Stands (N=184)*	4	*2.17	3	*1.63	1	*0.54	20	40
◆*Marked headlag (N=426)*	7	*1.64	3	*0.70	4	*0.94	4	8
◆*Truncal slump (N=299)*	10	*3.34	7	*2.34	3	*1.00	12	24

◆ Age-dependent variables. * Percentage calculated according to *N* in brackets.

Clinical signs with more than 5% of their observations not reported were: i) resistance to venesection, and ii) the ability of the patient to roll over. Both were used to assess weakness in patients. Data were not available since most patients had venesection before admission to the Unit and many patients were unwilling to roll over. For plasma sodium, patients' history of irritability for the current episode of diarrhoea was not reported in 25.9% of the patients. This was due to investigator error as a result of incorrect coding of questionnaires (Tables 4.8 and 4.9).

4.5.3 Reliability

There was substantial agreement between clinician pairs' in the assessment of the following clinical signs: abdominal distension (weighted Kappa score 0.70; 95% CI 0.49 to 0.91); ability to sit (weighed Kappa score 1.0; 95% CI 1.0 to 1.0); and to stand (weighed Kappa score 0.72; 95% CI 0.44 to 0.99). Clinicians had no agreement as to whether there was a wooden feel to the patients' skin (weighed Kappa score -0.02; 95%CI –1.24 to 1.21). All reliability assessments had broad confidence intervals (Tables 4.10 and 4.11). Contingency tables of raw data are presented in Appendix 4.5.

4.5.4 Diagnostic accuracy

4.5.4.1 Multi-level responses

Summaries of measures of diagnostic accuracy are shown in Tables 4.10 and 4.11 and contingency tables of the raw data in Appendices 4.6 to 4.10. None of the clinical signs showed clear clinical usefulness (LR greater than 5 or less than 0.20). Signs showing limited clinical meaningfulness (LR between 2 and 5 or 0.2 and 0.5) for plasma sodium and potassium abnormalities were: the presence of an ileus (LR 3.08; 95% CI 0.64 to 14.87) in hypokalaemic patients; the inability of a patient to sit (LR 2.15; 95% CI 1.12 to 4.13); lack of resistance during venesection (LR 3.22; 95% CI 1.48 to

7.00) and the presence of a truncal slump (LR 2.89; 95% CI 1.75 to 4.76) in severely hypokalaemic patients; and a wooden feel to the skin (LR 2.44; 95% CI 1.14 to 5.21) in hyponatraemic patients. Even though a depressed level of consciousness showed some association with hypernatraemia (LR 2.22; 95% CI 0.93 to 5.30) and hyponatraemia (LR 4.33; 95% CI 0.46 to 40.37), there was no gradient in LRs across the different levels of response. Poor peripheral perfusion was associated with: severe hypokalaemia (LR 3.11; 95% CI 1.18 to 5.16; n=512); severe hypernatraemia (LR 2.94; 95% CI 1.41 to 6.13; n=515); and hypernatraemia (LR 2.07; 95% CI 1.04 to 4.13, n=515. Ten percent dehydration on admission was associated with severe hypokalaemia (LR 2.13; 95% CI 1.07 to 4.25; n=519) and severe hypernatraemia (LR 2.00; 95% CI 0.46 to 8.68, n=522).

Good hydration showed some association with the absence of severe hypokalaemia (LR 0.40; 95% CI 0.17 to 0.90).

Table 4.10 Likelihood ratios and observer agreement (weighted Kappa) for clinical signs associated with sodium disturbances

Signs (n)	Severe hypernatraemia (sodium >158 mmol/l)		Hypernatraemia (sodium >150 mmol/l)		Hyponatraemia (sodium <135 mmol/l)		Weighted Kappa; [95%CI]
	LR	95% CI	LR	95% CI	LR	95% CI	
Level of consciousness (472)							0.66; [0.43 to 0.90]
(Glasgow Coma Score)							
<8	*	*Undefined	*	*Undefined	4.33	0.46 to 40.37	
8 ≤ 12	1.74	0.46 to 6.58	2.22	0.93 to 5.30	0.49	0.24 to 1.01	
>12	1.01	1.00 to 1.02	1.01	1.00 to 1.02	0.99	0.97 to 1.00	
Resists procedure (430)							-0.13; [-1.35 to 1.09]
Present	0.96	0.78 to 1.18	0.97	0.86 to 1.11	0.97	0.92 to 1.03	
Uncertain	1.75	0.63 to 4.86	1.35	0.59 to 3.12	0.84	0.51 to 1.38	
Absent	1.57	0.24 to 10.53	1.38	0.35 to 5.51	1.43	0.66 to 3.10	
Kicks away (470)							0.52; [0.06 to 0.97]
Present	0.92	0.69 to 1.24	0.86	0.67 to 1.10	0.98	0.90 to 1.07	
Uncertain	1.01	0.27 to 3.75	1.52	0.71 to 3.24	0.90	0.56 to 1.46	
Absent	1.38	0.50 to 3.82	1.73	0.89 to 3.38	1.09	0.71 to 1.68	

*Unable to calculate as the denominator was zero and the likelihood ratios approached infinity.

Table 4.10 (continued) Likelihood ratios and observer agreement (weighted Kappa) for clinical signs associated with sodium disturbances

Signs (n)	Severe hypernatraemia (sodium >158 mmol/l)		Hypernatraemia (sodium >150 mmol/l)		Hyponatraemia (sodium <135 mmol/l)		Weighted Kappa; [95%CI]
	LR	95% CI	LR	95% CI	LR	95% CI	
Pushes away (470)							0.50; [0.04 to 0.96]
Present	0.85	0.60 to 1.23	0.73	0.53 to 0.99	1.04	0.96 to 1.29	
Uncertain	1.66	0.70 to 3.95	1.24	0.59 to 2.62	0.82	0.54 to 1.27	
Absent	1.83	0.68 to 4.94	2.71	1.53 to 4.83	0.79	0.49 to 1.29	
Lifts head from bed (469)							0.64; [0.29 to 1.00]
Present	0.50	0.23 to 1.09	0.52	0.32 to 0.85	1.10	0.98 to 1.24	
Uncertain	2.69	1.11 to 6.51	1.61	0.69 to 3.76	0.74	0.42 to 1.31	
Absent	2.32	1.45 to 3.73	2.35	1.67 to 3.33	0.78	0.56 to 1.08	
Sits unsupported (298)							1.0; [1.0 to 1.0]
Present	1.13	1.09 to 1.18	0.64	0.34 to 1.21	1.04	0.95 to 1.13	
Uncertain	*	*Undefined	*	*Undefined	0.32	0.09 to 1.14	
Absent	*	*Undefined	3.97	1.58 to 9.96	0.75	0.39 to 1.44	
Rolls over (232)							0.27; [-0.30 to 0.85]
Present	1.22	*Undefined	0.81	0.37 to 1.79	0.93	0.82 to 1.05	
Uncertain	*	*Undefined	2.04	0.36 to 11.51	1.09	0.55 to 2.16	
Absent	*	*Undefined	1.90	0.37 to 9.71	1.41	0.77 to 2.60	

*Unable to calculate as the denominator was zero and the likelihood ratios approached infinity.

Table 4.10 (continued) **Likelihood ratios and observer agreement (weighted kappa) for clinical signs associated with sodium disturbances**

Signs (n)	Severe Hypernatraemia (sodium >158mmol/l)		Hypernatraemia (sodium >150mmol/l)		Hyponatraemia (sodium <135mmol/l)		Weighted Kappa; [95%CI]
	LR	95% CI	LR	95% CI	LR	95% CI	
Stands (180)							0.72; [0.44 to 0.99]
Present	1.39	*Undefined	0.69	0.26 to 1.83	088	0.72 to 1.06	
Uncertain	*	*Undefined	*	*Undefined	1.52	0.64 to 3.63	
Absent	*	*Undefined	1.81	0.66 to 4.99	1.42	0.85 to 2.38	
Wooden feel to skin (472)							-0.02; [-1.24 to 1.21]
Present	1.45	0.22 to 9.65	1.95	0.63 to 6.04	2.44	1.14 to 5.21	
Uncertain	4.15	1.40 to 12.37	1.94	0.61 to 6.13	1.02	0.47 to 2.21	
Absent	0.97	0.82 to 1.16	0.94	0.83 to 1.08	0.94	0.90 to 1.00	
Biceps, tendon reflexes (456)							0.21; [-0.26 to 0.68]
Brisk	1.45	0.60 to 3.52	1.43	0.70 to 2.93	0.78	0.44 to 1.37	
Normal	0.70	0.41 to 1.18	0.82	0.60 to 1.11	1.07	0.95 to 1.20	
Reduced	0.81	0.42 to 1.56	0.82	0.50 to 1.35	1.11	0.89 to 1.39	

*Unable to calculate as the denominator was zero and the likelihood ratio's approached infinity

Table 4.10 (continued) **Likelihood ratios and observer agreement (weighted kappa) for clinical signs associated with sodium disturbances**

Signs (n)	Severe hypernatraemia (sodium >158mmol/l)		Hypernatraemia (sodium >150mmol/l)		Hyponatraemia (sodium <135mmol/l)		Weighted Kappa; [95%CI]
	LR	95% CI	LR	95% CI	LR	95% CI	
Knee, tendon reflexes (458)							0.37; [0.03 to 0.70]
Brisk	1.34	0.75 to 2.40	1.55	1.08 to 2.24	0.72	0.50 to 1.03	
Normal	0.87	0.55 to 1.37	0.86	0.62 to 1.20	1.11	0.97 to 1.27	
Reduced	0.66	0.21 to 2.08	0.48	0.18 to 1.30	1.36	1.00 to 1.85	
Peripheral perfusion (515)							-
Poor	2.94	1.41 to 6.13	2.07	1.04 to 4.13	1.61	0.95 to 2.75	
Fair	0.63	0.27 to 1.50	0.80	0.48 to 1.33	1.61	1.29 to 2.01	
Good	0.71	0.46 to 1.09	0.84	0.66 to 1.07	0.92	0.82 to 1.02	
Degree of dehydration (522)							-
≥10%	2.00	0.46 to 8.68	1.90	0.58 to 6.13	1.28	0.45 to 3.6	
5%	1.50	1.01 to 2.22	1.27	0.87 to 1.84	1.10	0.85 to 1.4	
Potentially dehydrated	*	*Undefined	0.37	0.02 to 6.37	0.78	0.42 to 1.4	
Good	*	*Undefined	0.26	0 to 34530.3	0.77	0.11 to 5.16	

*Unable to calculate as the denominator was zero and the likelihood ratio's approached infinity

Table 4.10 (continued) Likelihood ratios for clinical signs associated with sodium disturbances

Signs (n)		Severe hypernatraemia (sodium >158mmol/l)		Hypernatraemia (sodium >150mmol/l)		Hyponatraemia (sodium <135mmol/l)	
		LR	95% CI	LR	95% CI	LR	95% CI
±History of irritability for current episode of diarrhoea (352)							
	Yes	1.31	1.11 to 1.56	1.18	0.96 to 1.43	0.78	0.67 to 0.92
	No	0.26	0.04 to 1.71	0.58	0.24 to 1.44	1.72	1.25 to 2.38
±History of seizures 24 hours pre-admission (471)							
	Yes	*	*Undefined	1.09	0.28 to 4.33	0.62	0.28 to 1.36
	No	1.07	1.04 to 1.09	0.99	0.90 to 1.09	1.03	0.98 to 1.08

± Weighted Kappa was not calculated for clinical assessments reported from patient's history.

*Unable to calculate as the denominator was zero and the likelihood ratio's approached infinity

Table 4.11 Likelihood ratios and observer agreement (weighted Kappa) for clinical signs associated with potassium disturbances

Signs (n)	Severe hypokalaemia (potassium <2.5 mmol/l)		Hypokalaemia (potassium <3.5 mmol/l)		Weighted Kappa [95%CI]
	LR	95% CI	LR	95% CI	
Level of consciousness (Glasgow Coma Score) (468)					0.66 [0.43 to 0.90]
<8	*Undefined	*Undefined	*Undefined	*Undefined	
8 ≤12	1.41	0.69 to 2.87	1.00	0.54 to 1.85	
>12	0.95	0.90 to 1.00	1.02	1.00 to 1.04	
Lies in a frog's legs position (465)					0.33; [-0.33 to 1.00]
Present	1.68	1.01 to 2.79	1.27	0.79 to 2.01	
Uncertain	1.56	0.92 to 2.63	1.30	0.81 to 2.10	
Absent	0.90	0.79 to 1.02	0.96	0.88 to 1.04	
Marked headlag (419)					0.65, [0.35 to 0.95]
Present	1.99	1.48 to 2.66	1.36	0.99 to 1.85	
Uncertain	1.06	0.62 to 1.82	1.39	0.88 to 2.19	
Absent	0.65	0.50 to 0.84	0.87	0.76 to 1.00	
Truncal slump (289)					0.49; [- 0.21 to 1.18]
Present	2.89	1.75 to 4.76	1.32	0.77 to 2.27	
Uncertain	1.31	0.73 to 2.36	1.45	0.81 to 2.59	
Absent	0.72	0.59 to 0.89	0.94	0.84 to 1.06	

*Unable to calculate as the denominator was zero and the likelihood ratios approached infinity.

Table 4.11 (continued) **Likelihood ratios and observer agreement (weighted Kappa) for clinical signs associated with potassium disturbances**

Signs (n)		Severe hypokalaemia (potassium <2.5 mmol/l)		Hypokalaemia (potassium <3.5 mmol/l)		Weighted Kappa [95%CI]
		LR	*95% CI*	*LR*	*95% CI*	
Resists procedure (427)						-0.13; [-1.35 to 1.09]
	Present	0.89	0.79 to 0.99	0.96	0.91 to 1.02	
	Uncertain	2.35	1.45 to 3.85	1.49	0.91 to 2.43	
	Absent	3.22	1.48 to 7.00	1.73	0.78 to 3.86	
Kicks away (466)						0.52 [0.06 to 0.97]
	Present	0.83	0.71 to 0.97	0.93	0.85 to 1.01	
	Uncertain	2.02	1.25 to 3.26	1.04	0.65 to 1.65	
	Absent	1.98	1.26 to 3.11	1.44	0.93 to 2.23	
Pushes away (466)						0.50 [0.04 to 0.96]
	Present	0.84	0.72 to 0.98	0.98	0.91 to 1.07	
	Uncertain	2.20	1.46 to 3.33	1.36	0.90 to 2.07	
	Absent	2.10	1.28 to 3.45	1.09	0.68 to 1.74	
Lifts head from bed (465)						0.64 [0.29 to 1.00]
	Present	0.77	0.63 to 0.95	1.00	0.89 to 1.13	
	Uncertain	1.39	0.76 to 2.55	1.03	0.61 to 1.75	
	Absent	1.66	1.21 to 2.29	0.99	0.73 to 1.34	

Table 4.11 (continued) Likelihood ratios and observer agreement (weighted Kappa) for clinical signs associated with potassium disturbances

Signs (n)		Severe hypokalaemia (potassium <2.5 mmol/l)		Hypokalaemia (potassium <3.5 mmol/l)		Weighted Kappa [95%CI]
		LR	95% CI	LR	95% CI	
Sits unsupported (295)						1.0; [1.0 to 1.0]
	Present	0.89	0.79 to 1.00	1.00	0.92 to 1.09	
	Uncertain	0.95	0.27 to 3.34	1.19	0.40 to 3.56	
	Absent	2.15	1.12 to 4.13	0.97	0.50 to 1.86	
Rolls over (231)						0.27 [-0.30 to 0.85]
	Present	0.94	0.79 to 1.11	1.02	0.90 to 1.17	
	Uncertain	1.28	0.60 to 2.72	1.40	0.68 to 2.88	
	Absent	1.29	0.68 to 2.46	0.91	0.51 to 1.63	
Stands (180)						0.72; [0.44 to 0.99]
	Present	0.78	0.58 to 1.04	0.82	0.68 to 0.99	
	Uncertain	2.06	0.90 to 4.71	3.44	1.05 to 11.31	
	Absent	1.67	1.02 to 2.73	1.74	0.99 to 3.04	
Ileus (467)						0.48; [-0.003 to 0.97]
	Present	1.52	0.32 to7.29	3.08	0.64 to14.87	
	Uncertain	2.15	1.00 to 4.63	1.46	0.69 to 3.08	
	Absent	0.99	0.95 to 1.03	0.98	0.96 to1.01	

Table 4.11 (continued) **Likelihood ratios and observer agreement (weighted Kappa) for clinical signs associated with potassium disturbances**

Signs (n)	Severe hypokalaemia (potassium <2.5 mmol/l)		Hypokalaemia (potassium <3.5 mmol/l)		Weighted Kappa [95%CI]
	LR	95% CI	LR	95% CI	
Abdominal distension (470)					0.70; [0.49 to 0.91]
Present	1.43	0.77 to 2.67	1.58	0.92 to 2.73	
Uncertain	1.88	1.02 to 3.46	2.07	1.12 to 3.82	
Absent	0.95	0.86 to 1.05	0.95	088 to 1.01	
Peripheral perfusion (512)					-
Poor	3.11	1.88 to 5.16	1.52	0.89 to 2.58	
Fair	1.46	1.16 to 1.84	1.42	1.12 to 1.78	
Good	0.71	055 to 0.90	0.93	0.85 to 1.02	
Degree of dehydration (519)					-
≥10%	2.13	1.07 to 4.25	1.64	0.53 to 5.07	
5%	1.14	0.98 to 1.324	1.22	0.93 to 1.60	
Potentially dehydrated	0.51	0.39 to 0.67	0.64	0.35 to 1.15	
Good	0.40	0.17 to 0.90	0.56	0.08 to 3.81	

4.5.4.2 *Binary responses*

Sensitivity and specificity were calculated for signs with a binary response, namely, i) irritability (history of crying during the current episode of diarrhoea) for increased levels of plasma sodium, and ii) history of seizures in the last 24 hours prior to admission to the Rehydration Unit for increased and decreased levels of plasma sodium. Irritability was sensitive for severe hypernatraemia (92% sensitive) but not specific (30% specific). The same was noted for hyponatraemia (60% sensitive, 23% specific). History of seizures was more specific than sensitive in patients with plasma sodium disturbances: hyponatraemia (4% sensitivity, 93% specific), hypernatraemia (6% sensitivity, 94% specific) and severe hypernatraemia (94% specific, unable to assess sensitivity as no severely hypernatraemic patients had seizures) (Table 4.12).

Both irritability and seizures had large negative predictive values for severe hypernatraemia (99% and 97% respectively), and hypernatraemia (96% and 93% respectively). Negative predictive values for hyponatraemia were 51% with irritability and 60% with seizures (Table 4.12).

4.5.4.3 *Logistic regression analysis*

Logistic regression analysis was not performed as none of the clinical signs showed statistical significance and clinical meaningfulness (LR >5 or <0.2).

Table 4.12 Measures of diagnostic accuracy of binary responses for abnormal sodium levels

	History of irritability for current episode of diarrhoea			
	Sensitivity (%)	**Specificity (%)**	**Positive predictive value (%)**	**Negative predictive value (%)**
Severe hypernatraemia (sodium >158 mmol/l)	92	30	5	99
95% CI	64.0 to 99.8	24.9 to 34.7	2.5 to 8.2	94.7 to 100
Hypernatraemia (sodium >150 mmol/l)	83	30	8	96
95% CI	61.2 to 95.1	24.8 to 34.7	4.6 to 11.6	90.3 to 98.9
Hyponatraemia (sodium <135 mmol/l)	60	23	30	51
95% CI	51.8 to 68.9	17.5 to 28.5	24.7 to 36.1	41.3 to 60.7

Table 4.12 (continued) Measures of diagnostic accuracy of binary responses for abnormal sodium levels

	History of seizures in the last 24 hours pre-admission			
	Sensitivity (%)	**Specificity (%)**	**Positive predictive value (%)**	**Negative predictive value (%)**
Severe hypernatraemia (sodium >158 mmol/l)	0	94	0	97
95% CI	0 to 21.8	91.2 to 95.9	0 to 12.3	94.5 to 98.1
Hypernatraemia (sodium >150 mmol/l)	6	94	7	93
95% CI	0.79 to 21.4	91.5 to 96.1	0.87 to 23.5	90.7 to 95.6
Hyponatraemia (sodium <135 mmol/l)	4	93	29	60
95% CI	1.9 to 8.3	89.4 to 95.7	13.2 to 48.7	55.5 to 64.6

4.6 Discussion

4.6.1 Interpretation of the principal findings

In general, clinical signs were neither useful nor reliable in actual practice at any pre-specified cut-off level. Some of the signs were unhelpful because they could not easily be performed, both in the study of reliability and of diagnostic accuracy (Table 4.8 and 4.9). Examples of these were: i) assessing the patient's ability to roll over and/or sit and/or stand; ii) whether the patient had a truncal slump; and iii) assessment of the tendon reflexes. The practical application of these signs was difficult. Reliability of the signs was most often low and probably contributed to the poor diagnostic accuracy (Bossuyt *et al.*, 2003).

4.6.1.1 Reliability of the clinical signs

Signs that were shown to be reliable in clinical practice were ability to sit (100% agreement), stand (72% agreement) and abdominal distension (70% agreement). The 95% confidence intervals for these estimates were broad, making interpretation difficult. For example, clinician pairs could have anything between 49% to 91% agreement as to whether a patient's abdomen was distended. An anomaly observed in the reliability study was that clinicians were in complete agreement about whether a patient could sit (weighed Kappa score 1; 95% CI 1 to 1). This sign was not assessed in 24% of the patients (Table 4.8 and 4.9) and may therefore be spurious; it should be interpreted with caution. Even though a wooden feel to the skin is stated in literature (Rudzinski *et al.*, 1996:342) to indicate hypernatraemia, this study showed that the reliability of this sign (-0.02%; 95%CI –1.24 to 1.21) was extremely poor (no agreement between medical officers).

The setting for the reliability study could mean that the generally poor agreement is actually an overestimate of that in actual clinical practice. Two of the three doctors in the reliability study had been part of the study of

diagnostic accuracy and were thus familiar with the study protocol. The third doctor was currently involved in research and understood the importance of accurately reporting the clinical signs. She had also recently worked in the Rehydration Unit. All three doctors performed clinical assessments in their free time (with no other competing responsibilities) and were compensated financially for their assistance. They were thus provided with an incentive to perform the assessments to the best of their ability resulting in an improved accuracy of the findings.

Although operational definitions for signs were given when thought appropriate, no training was provided in eliciting the signs. These findings represent actual practice in a well-resourced teaching hospital in a middle-income country and reliability is unlikely to be better in actual practice elsewhere, where larger caseloads could reduce reliability. This low reliability is expected to compromise diagnostic accuracy.

4.6.1.2 Diagnostic accuracy of clinical signs

The findings on the diagnostic accuracy of the clinical signs need to be interpreted in the light of the reliability of the signs reported in section 4.6.1.1. None of the clinical signs had LRs that were greater than 5 or less than 0.2. Even when LRs were estimated potentially clinically meaningful (LR between 2 and 5 or 0.2 and 0.5), there was often no gradient with different levels of response. That is, there was no progression in the size of the LR from negative to equivocal to positive. An example of this is a wooden feel to the skin in severely hypernatraemic patients: the presence of a wooden feel to the skin had an LR of 1.45 and the absence of the sign an LR of 0.97, while the equivocal level had an LR of 4.15. This probably reflects low statistical power and caution should be used when interpreting such findings since they could be due to chance.

The lack of statistical power is also illustrated in the wide 95% confidence intervals for some of the signs. Even though the presence of an ileus showed

some association with patients that were hypokalaemic (LR 3.08; 95% CI 0.64 to 14.87), the 95% confidence intervals were broad, indicating that the result could be due to chance. This was also true for the association between 10% dehydration on admission and severe hypernatraemia (LR 2.00; 95% CI 0.46 to 8.68, n=522). In these cases, however, the broad 95% confidence intervals are partly due to the low prevalence of the sign (ileus; 1.7%) or of the target condition (severe hypernatraemia; 3.2%).

Even when signs showed a statistically significant or more precise estimate, association with the target condition was not clinically meaningful. This was the case for the associations of a patient's inability to sit (LR 2.15; 95% CI 1.12 to 4.13) with severe hypokalaemia; poor peripheral perfusion with severe hypokalaemia (LR 3.11; 95% CI 1.88 to 5.16; n=512), severe hypernatraemia (LR 2.94; 95% CI 1.41 to 6.13; n=515) and hypernatraemia (LR 2.07; 95% CI 1.04 to 4.13; n=515); and being 10% dehydrated on admission with severe hypokalaemia (LR 2.13; 95% CI 1.07 to 4.25; n=519). For example, poor peripheral perfusion showed a statistically significant relationship with severe hypokalaemia and had a relatively high LR. However, the probability of severe hypokalaemia in the sample as a whole was 18.9%, in those with poor peripheral perfusion 42.2%, in those with equivocal perfusion 25.4% and in those with good perfusion 14.2%. Thus peripheral perfusion has limited usefulness in distinguishing severely hypokalaemic children from other children. Similarly, poor peripheral perfusion had an LR of 2.94 for severe hypernatraemia, which had a prevalence of 3.2% in the sample as a whole, meaning that only 8.8% of the patients that had poor peripheral perfusion and about 2.2% of the patients that had good peripheral perfusion were actually severely hypernatraemic. These examples illustrate the limited clinical usefulness of peripheral perfusion as a sign to distinguish i) patients with plasma sodium disturbances from those that are normal, ii) patients with plasma potassium disturbances from those that are normal, and iii) patients with plasma sodium and potassium disturbances from each other in children with diarrhoea in the study setting.

The absence of dehydration showed some clinical association with severe hypokalaemia (LR 0.40; n=519). With an overall prevalence of 18.9% in this sample, the presence of good hydration would therefore lower the probability of severe hypokalaemia to 8.5%. If it is judged acceptable to miss severe hypokalaemia in 8.5% of cases, good hydration could be regarded as a useful sign of severe hypokalaemia at this prevalence. However, this finding has limited usefulness in a ward designed for children who are not well hydrated.

History of irritability for the current episode of diarrhoea (with a binary response) had a high sensitivity (92%) for severe hypernatraemia, but a low specificity (30%). Absence of irritability thus makes severe hypernatraemia unlikely (negative predictive value in the sample 99%), but the presence of irritability has a poor positive predictive value (5%) because of the low specificity of the test and the low prevalence of severe hypernatraemia (3.2%) in the current study.

In contrast, a history of seizures within 24 hours prior to admission had a high specificity (94%) for hypernatraemia, but a low sensitivity (6%). Absence of seizures thus makes severe hypernatraemia unlikely (negative predictive value in the sample 93%), but the presence of seizures has a poor positive predictive value (7%), this time because of the low sensitivity of the test and the low prevalence of hypernatraemia (6.5%).

Interestingly, the low prevalence of hypernatraemia in the current study results in low positive predictive values and high negative predictive values for both tests, with markedly contrasting sensitivities and specificities. This illustrates the importance of prevalence of the target condition in interpreting the test results. As the prevalence of the condition decreases, so does the positive predictive value. Due to the low prevalence of most target conditions in the current study (except hyponatraemia and hypokalaemia), positive predictive values were generally low. For example, as tests for hypernatraemia, the positive predictive value for irritability was 8% and for

history of seizures 7%. This implies the need for 13 and 14 confirmatory tests respectively in order to correctly identify one case of hypernatraemia in the study setting compared to 15 tests, if testing was performed routinely on all admissions. Use of the clinical signs to marginally reduce the number of tests to detect one abnormality would be counter-balanced by missing some cases of hypernatraemia. In the case of history of seizures, 94% of all cases would be missed (sensitivity of 6%). These examples illustrate the principle that, unless very accurate, diagnostic tests are of limited usefulness for conditions of low prevalence (Sackett *et al.*, 1991:91).

The low prevalence of the severe electrolyte disturbances thus has two important implications for the interpretation of the findings. Firstly, there is uncertainty around the point estimates of accuracy (wide 95% CI), because of low statistical power. Secondly, taking this uncertainty into account, none of the clinical signs appear sufficiently accurate to be useful in these conditions of very low prevalence. For example, the higher upper 95% CI for the estimate of the LR for a positive test for a wooden feel to the skin for severe hypernatraemia was 9.7. The presence of a wooden feel to the skin, with this LR, would increase the probability of severe hypernatraemia to only 24.3%.

4.6.2 Comparison with past studies

Even though no studies were identified that explicitly studied the diagnostic accuracy of clinical signs for plasma sodium and potassium disturbances, data were extracted from two reports (Hill *et al.*, 1981 and Tjon A Ten, 1999), and measures of diagnostic accuracy were calculated (see section 4.1.1).

The estimates calculated from data extracted from Hill *et al.* (1981) showed a statistically significant, clinically meaningful association with hypernatraemia for coma/convulsions/drowsy (LR 7.77; 95% CI 1.98 to 30.48; specificity 96%, sensitivity 31%, positive predictive value 95%, negative predictive value 35%) (Table 4.1). Being jittery was 100% specific, with a positive predictive

value of 100% for hypernatraemia. Comparison of these estimates and the current research is difficult since no description of how signs were defined and/or elicited was reported and no signs appeared directly comparable. However, the accuracy of coma/convulsions/drowsy appears to be significantly better than for level of consciousness reported in the current study. Elements of study design in the Hill *et al.* (1981) study could have introduced potential bias, resulting in an overestimate in the findings. These elements have been reported in section 4.1.1 and can be summarised as selection bias, spectrum bias and test review bias (see glossary). The current study has been designed to eliminate these potential sources of bias, and this is reported under the "strengths of the research" (section 4.6.4).

Calculations based on data extracted from the study performed by Tjon A Ten (1999) are likely to over-estimate accuracy because of the considerable assumption that all (presumably less dehydrated) cases without serum sodium measurements had a normal serum sodium levels. Despite this, the LR calculated from extracted data indicated that it was not clinically meaningful (LR 4.30, 95% CI 1.07 to 17.30) (Table 4.2). Comparison between Tjon A Ten (1999) and the current study is difficult as different definitions were used for dehydration and different spectra of patients were assessed in both studies, as mentioned in section 4.1.1. Again, Tjon A Ten's (1999) findings have limited applicability to the current study setting, since their study was conducted in the developed world (Holland), where the prevalence of sodium disturbances were lower (a 3% prevalence of hypernatraemia over a period of five years in Holland compared to 6.5% over a period of one year in the current study). Also, unclear reporting of the study methodology made appraisal of the validity of the findings difficult for Tjon A Ten's (1999) study and broad 95% confidence intervals implied that the finding could be due to chance.

4.6.3 Generalisability of the findings

Although operational definitions for signs were given when thought appropriate, no training was provided in eliciting the signs. The findings thus represent actual practice in a well-resourced teaching hospital in a middle-income country and accuracy is unlikely to be better in actual practice elsewhere in low- and middle-income countries.

The estimates of sensitivity, specificity and the LRs are likely to be applicable to similar groups of children, but estimates of predictive values are limited to a setting with the same prevalence of plasma sodium and potassium disturbances as in the current study.

4.6.4 Strengths of the research

The sample of patients in this study is broadly representative of children admitted to diarrhoeal rehydration units in metropolitan Cape Town. This not only increases the generalisability of the findings but also provided a clinically meaningful spectrum of patients (that is, children were not selected by the presence or absence of the plasma sodium and potassium disturbances, demographic features and co-morbidities), thus minimising spectrum bias (see glossary).

A prospective, consecutive sample (during specified hours) of patients was enrolled into the study, reducing selection bias (see glossary).

Laboratory testing of plasma sodium and potassium levels (reference standard) were not done on the basis of the presence or absence of clinical signs, and vice versa, minimising verification bias (see glossary).

In both the reliability study and the study of diagnostic accuracy, all clinical assessments were performed with the medical officers blinded to the plasma sodium and potassium levels of the patient. This reduced the possibility of

test review bias (see glossary) that distorts (over-estimates) the measures of diagnostic accuracy of the clinical sign because of knowledge of the result of the reference standard. Also, in the reliability study, the medical officers were unaware of their colleague's assessment of the clinical signs.

The assessments of clinical signs were done by a wide range of medical officers (56) in actual practice, making the results a reasonable reflection of current practice in a teaching hospital in a middle-income country. However, many medical officers were junior doctors in competition for longer-term employment at Red Cross Children's Hospital and may have performed their jobs with greater vigilance and care than average. This could have resulted in an over-estimation of accuracy in other settings in low-and middle-income countries.

4.6.5 Limitations of the research

Because of the shortfall in numbers targeted for enrolment, the findings could be limited by lack of power to detect meaningful diagnostic accuracy for less prevalent conditions, for example; hypernatraemia, severe hypernatraemia and severe hypokalaemia. The lack of evidence of diagnostic accuracy thus does not necessarily constitute evidence of lack of accuracy. The consistent pattern of low accuracy across all tests, however, provides an additional indication of unhelpful accuracy.

Lack of statistical power was most evident for conditions of low prevalence. Because diagnostic test results are clinically less meaningful at low prevalence of the target condition (Sackett *et al.*, 1991:91), tests for these conditions appear likely to be of limited value, even if their accuracy was substantially higher than expected. The lack of meaningful clinical association (even though there is some association) between severely hypokalaemic patients and the age-dependent signs of sitting (n=295) and/or a truncal slump (n=289) could be a result of the small sample available for analysis; even so, the 95% CI were all below 5 and were narrow.

The current study was of clinical signs as elicited in actual practice. The possibility that accuracy could be improved by careful operational definitions and training in the detection of the signs was not addressed by this study.

4.6.6 Implications for practice

No clinical signs (as defined in the study) were identified that were clinically useful in actual practice. Although meaningful diagnostic accuracy has not been excluded for all signs examined, none appear likely to be useful at the low prevalence of severe abnormalities in children with diarrhoea.

The 'negative' findings in this study of the poor diagnostic accuracy of commonly used clinical signs further add to the importance of the findings, in that many of the signs assessed are currently, though misleading, used in everyday practice.

Considerable caution should thus be used when interpreting these clinical signs. False positive signs will carry the potentially harmful effects and expense of unnecessary treatment or transfer of patients. False negative signs will result in the potentially harmful effects of the disorders not being treated.

Unless the accuracy of the signs can be improved by clearer definition and/or training (see Section 4.6.7), alternative approaches to reliance on clinical signs may need to be considered. In settings where resources permit, routine electrolyte testing of children admitted to hospital with diarrhoea may need to be considered. Where resources do not permit, adjustment of standard clinical procedures, such as the use of more supplemental oral potassium for all admitted patients, needs consideration, taking the specific conditions of each setting into account.

4.6.7 Implications for research

It is possible that clearer definitions of clinical signs could improve the reliability and validity of these signs. A study incorporating these features would be required to demonstrate this.

Alternatively, strategies to avoid reliance on clinical testing need to be investigated. These could include routine electrolyte testing of children admitted to hospital with diarrhoea (see Study 3 in Chapter 5), or the use of more supplemental oral potassium for all admitted patients.

4.7 Conclusion

This is the first systematic study of the diagnostic accuracy of clinical signs of plasma sodium and potassium disturbances in children with diarrhoea. The clinical signs assessed were neither useful nor reliable in clinical practice. Although there is uncertainty around the estimates of diagnostic accuracy for less prevalent conditions like hypernatraemia, severe hypernatraemia and severe hypokalaemia because of low statistical power, the most optimistic plausible levels of accuracy are not clinically meaningful, given the low prevalence of the target conditions. The lack of evidence of diagnostic accuracy therefore does not necessarily constitute evidence of lack of accuracy.

These findings are based on the elicitation of the signs in usual practice. Training of practitioners in how to elicit signs could increase the reliability and accuracy of these signs.

CHAPTER FIVE: THERAPEUTIC IMPACT OF ROUTINE ELECTROLYTE MEASUREMENTS ON MANAGEMENT OF ABNORMAL PLASMA SODIUM AND POTASSIUM LEVELS IN CHILDHOOD DIARRHOEA

5.1 Background

Routine electrolyte testing of children with dehydrating diarrhoea is usually not possible in settings where diarrhoea is more prevalent, due to the lack of testing facilities. However, when facilities to perform such testing are available, electrolytes are liberally tested. Ninety percent of the children being admitted to the Rehydration Unit at Red Cross Children's Hospital have their electrolytes tested on admission (Swingler, G. 2005. Personal Communication. 17 March, Institute of Child Health, Cape Town), and routine testing for inpatients is implied by the Standard Treatment Guidelines of the Essential Drugs Programme for hospital level paediatrics in South Africa (Essential Drugs Programme South Africa, 1998:13, 14). A report prepared by the Maryland School of Medicine (USA) also emphasised routine electrolyte testing as a part of the physical examination in the management of diarrhoea (Woodward & Woodward, 1986).

The potential benefits of such testing are the detection of otherwise undetected and potentially fatal abnormalities, enabling correction of the abnormality and prevention of potential morbidity or death. However, in the developing world, where dehydrating diarrhoeal disease is more prevalent, few medical facilities have on-site laboratories or even access to any laboratory facilities to perform such testing. The costs of electrolyte testing include: i) a distressing process for the parent who often has to leave the examination room, ii) the discomfort of venesection to the child, and iii) the financial costs to the service. The financial costs encompass: i) the costs of the tests and materials to perform the tests; ii) the time of the clinician and nursing sister required to perform the test; iii) the transport of the blood

specimens to the laboratory for analysis, and iv) the time of the laboratory technician to determine the blood result and convey that information to the clinician either telephonically or via the hospital's central computer data base. If the practice does produce benefit, it is important to determine the size of the benefit so that the need for the extension of testing facilities can be weighed against the costs and competing claims on scarce resources. If there is no clinical benefit from such testing, it should be discontinued because of the wastage of already limited financial resources (particularly in the developing world), the discomfort to the child and the distress to the parent.

5.1.1 Review of the literature for reports on therapeutic impact of routine electrolyte testing

5.1.1.1 Identification of relevant studies

A PubMed search (search strategy reported in Appendix 5.1) was performed for the period 1966 to May 2005. Two-hundred studies were identified in the search. The abstracts of these studies were screened by the principal investigator to identify those that met the criteria of reporting on i) the therapeutic impact of ii) routine electrolyte testing when managing iii) children with diarrhoea. Twenty-one studies were deemed possibly relevant and full reports were obtained, to enable fuller assessment. The reference lists of identified studies were also screened for potentially relevant reports.

5.1.1.2 Results of the literature review

After reading full reports of articles that were potentially eligible for inclusion, one study was found that met the inclusion criteria detailed in Section 5.1.1.1. This single study (Tjon A Ten, 1999) took place in a hospital in Holland and reported on the frequency and management of electrolyte disturbances in children with acute diarrhoea admitted to the hospital between January 1992 and December 1999. A total of 265 patients were enrolled, of whom 8 (3%)

had serum sodium levels >150 mmol/l, 1 (0.4%) a serum sodium level <130 mmol/l and 1 a serum potassium level <3.0 mmol/l. Sodium abnormalities were more common in dehydrated than non-dehydrated children, for example, with hypernatraemia 5 (1.9%) were dehydrated and 3 (1.1%) were non-dehydrated and with hyponatraemia 1 (0.4%) was dehydrated and none were non-dehydrated. The only potassium abnormality found was in a dehydrated patient. The author concluded that measuring electrolytes in children with acute diarrhoea was not necessary in all cases, but could be useful in dehydrated children. This study also found that when abnormally low levels of electrolytes were reported, it seldom led to changes in treatment. Only the single case with hypokalaemia had treatment changed based on the laboratory results (*ibid*). The number needed to be tested to identify one patient with hypokalaemia was 265 (95% CI –277 to 90). Due to the low prevalence of hypokalaemia, this estimate was not statistically significant. This study was performed in an industrialised setting where only 74 (27.9%) of the children were presumably mildly dehydrated and electrolyte abnormalities were less prevalent than expected in sicker children, reducing the applicability of the findings in settings where dehydrating diarrhoea is more prevalent.

The overall benefit or harm of routine electrolyte testing needs to be established in a setting where dehydration and plasma sodium and potassium disturbances in children with diarrhoea are more prevalent. Clinical benefit would require a change in clinical management as a result of routine electrolyte testing.

5.2 Aim of study

This study aimed to perform an exploratory assessment of the amount of change in clinical management as a result of routine electrolyte testing in children admitted to hospital for diarrhoea in a developing country.

5.3 Objectives

To determine the proportion of children with dehydrating diarrhoeal disease who are routinely tested for electrolyte abnormalities and in whom i) abnormalities are detected and ii) clinical management is changed as a result of the abnormalities.

5.4 Methods

5.4.1 Inclusion and exclusion criteria

All patients enrolled in the studies described in Chapters Three and Four were included (see sections 3.4.1 and 4.4.1). There were no additional inclusion or exclusion criteria for enrolment into this study. Therefore the caregivers of all patients between 6 weeks and 2 years of age admitted to the Rehydration Unit at Red Cross Children's Hospital during working hours were approached to participate in the study. Patients excluded were those that i) had any neurological disorders, for example, cerebral palsy or developmental delay; ii) were taking diuretics as part of their treatment regimen on admission; or iii) had been residing in the Cape metropolis for less than 1 month.

5.4.2 Sampling

The same sampling technique used to enroll patients in the studies outlined in Chapters Three and Four was used. This technique is described in section 2.3.

5.4.3 Measurement of outcomes and data collection

Clinical practice in the Rehydration Unit was specified by a clinical protocol. The prescribed management for plasma sodium and potassium abnormalities

for the duration of this study is shown in Appendix 5.2. The outcomes for this study were thus taken as the management prescribed (in the clinical notes) that: i) was consistent with protocol management of electrolyte abnormalities on admission of the patient and ii) could feasibly be measured retrospectively from the clinical notes (Appendices 5.3 and 5.4).

The specified management changes investigated in this study were:

- *potassium less than 3.0 mmol/l:*
  prescribed oral daily dose of potassium above 1.5 g (all ages) in the first 24 hours after admission (a higher dose than routinely prescribed on admission);
- *potassium less than 2.0 mmol/l and less than 1.0 mmol/l:*
  oral potassium chloride (KCl) as above and intravenous fluid containing more than 17 mmol/l of potassium (this is not given if potassium $\geq$2 mmol/l). The concentration in the routinely administered half dextrose Darrows solution is 17 mmol/l;
- *plasma sodium less than 125 mmol/l:*
  intravenous fluid containing more than 51 mmol/l of plasma sodium (the concentration in the routinely administered half dextrose Darrows solution is 51 mmol/l);
- *plasma sodium more than 155 mmol/l:*
  performance of at least one further plasma sodium measurement.

The principal investigator extracted electrolyte results from routine laboratory records (see Appendix 3.2). Management was assessed by examination of the routine clinical records to identify the pre-specified management changes recorded in the file that were consistent with the treatment protocol for the electrolyte abnormalities occurring in that patient. The *pro forma* structure of the clinical notes used in the Rehydration Unit facilitated the extraction of data (Appendix 5.3). Only treatment procedures recorded in the clinical records were included.

5.4.4 Analysis

Methods of estimation rather than hypothesis testing were used for a more meaningful analysis of the amount of management change to be expected in different settings. The proportion (with 95% CI) of patients in whom management was changed was calculated for each electrolyte abnormality individually, and also for all electrolyte disturbances combined. The number needed to test (see glossary) (with 95% CI) was reported, to give an indication of the amount of effort required to identify one patient with the target condition of interest in whom management was changed.

5.5 Results

A total of 2270 patients with diarrhoea were admitted to the Rehydration Unit at Red Cross Children's Hospital from 1 April 2002 to 31 March 2003 (data from unpublished routine hospital records). Five hundred and thirty-five patients between the ages of 6 weeks and 2 years were enrolled into the study (Figure 5.1) for the period 15 April 2002 to 14 April 2003. Of these five patients had neither plasma sodium nor plasma potassium levels measured on admission and were thus excluded from the study. The median age was 16.5 months (inter-quartile range 9.7-23.5 months). Two hundred and twelve patients (40.0%) had some *co-morbidity. Most of the patients (63.3%) were 5% dehydrated or more. Other patient characteristics are reported in Table 5.1. Plasma sodium levels were available for 528 (99.6%) patients and plasma potassium for 525 (99.1%) patients. The proportions of children with electrolyte disturbances are shown in Table 5.2.

Missing data: *Co-morbidity 176 [33.2%]

Figure 5.1 Profile of enrolment – impact of routine electrolyte measures

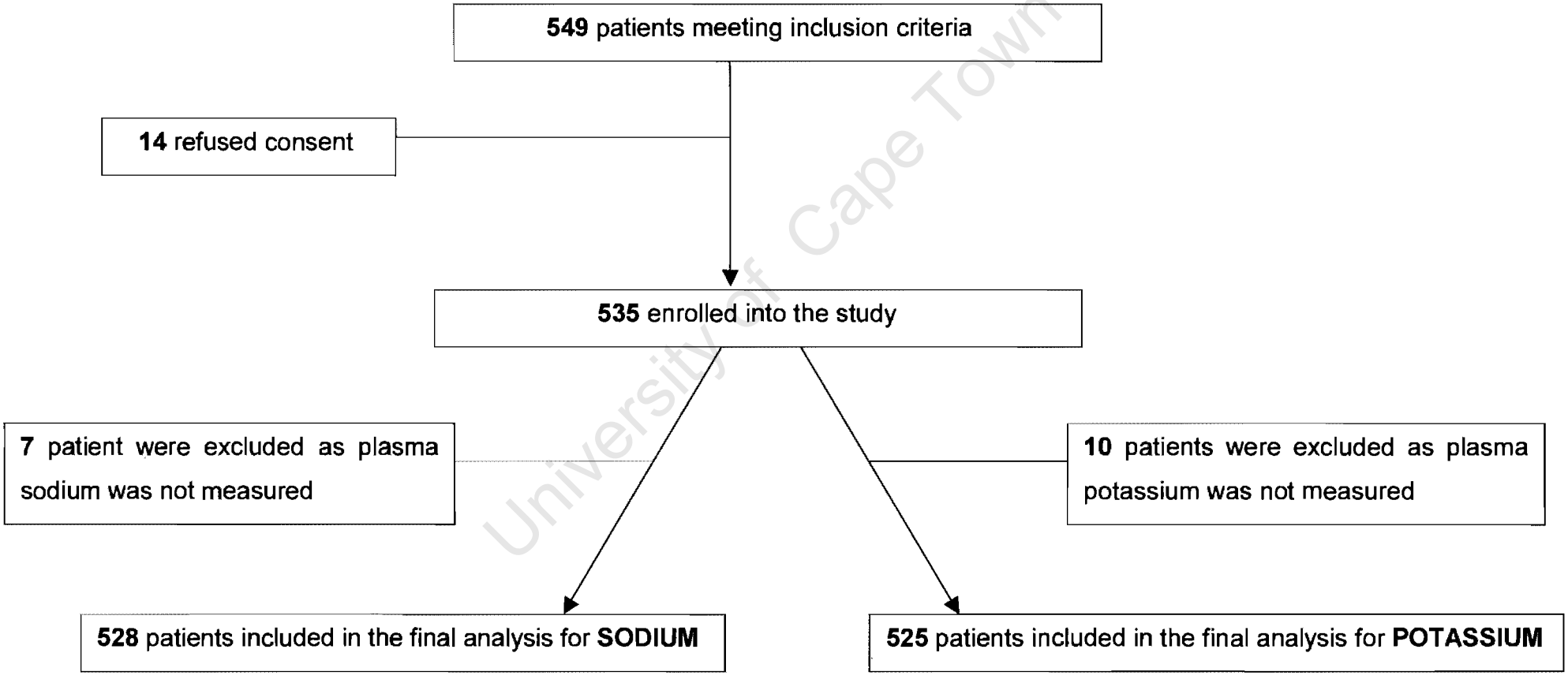


Table 5.1 Characteristics of patients included in the analysis (N=530)

Nutrition n (%)	Hydration n (%)	Peripheral perfusion n (%)	Gender n (%)
Marasmus/Kwashiorkor	≥ 10% dehydrated	Poor	Males
1 (0.2)	80 (15.1)	46 (8.7)	289 (54.5)
Kwashiorkor	5% dehydrated	Fair	Females
8 (1.5)	250 (47.2)	191 (36.0)	241 (45.5)
Marasmus	Potentially dehydrated	Good	
47 (8.9)	143 (27.0)	280 (52.8)	
Under-weight for age	Good hydration		
142 (26.8)	51 (9.6)		
Normal			
258 (48.7)			

Missing data: Nutrition (74 [14.0%]), hydration (6 [1.1%]), peripheral perfusion (13 [2.5%]).

5.5.1 Identification of abnormalities

Testing identified 55 (10.4%) with abnormal plasma sodium levels, 18 (3.4%) of which were below 125 mmol/l, 37 (7.0%) above 150 mmol/l and 23 (4.4%) above 155 mmol/l. One hundred and sixty-six patients (31.6%) had low potassium levels; with 40 (7.6%) below 2 mmol/l and 13 (2.5%) below 1.5 mmol/l (Table 5.2).

Table 5.2 Proportions of patients with electrolyte abnormalities and the number needed to test (NNT) in order to detect such an abnormality

Target condition	n (%) of N	95% CI	NNT	95% CI
Plasma sodium < 125 mmol/l	18 (3.41)	[2.03 to 5.33]	29	[20-54]
Plasma sodium > 150 mmol/l	37 (7.01)	[4.90 to 9.50]	14	[11-21]
Plasma sodium > 155 mmol/l	23 (4.36)	[2.78 to 6.46]	23	[16-38]
Potassium < 3 mmol/l	166 (31.60)	[27.6 to 35.6]	3	[3-4]
Potassium < 2 mmol/l	40 (7.62)	[5.5 to 10.2]	13	[10-19]
Potassium < 1.5 mmol/l	13 (2.48)	[1.32 to 4.19]	40	[26-87]

N for plasma sodium = 528; N for plasma potassium = 525.

Twenty-nine patients needed to be tested to identify one patient with plasma sodium below 125 mmol/l, and 23 for a plasma sodium level above 155 mmol/l. Three to four patients needed testing in order to identify one patient with hypokalaemia, 13 patients to identify one patient with a potassium level below 2 mmol/l and 40 to identify one patient with a potassium level below 1.5 mmol/l.

5.5.2 Change in management as a result of testing

5.5.2.1 Plasma sodium abnormalities

Of the 18 patients with plasma sodium levels below 125 mmol/l, 11 (61.1%, 95% CI 35.7% to 82.7%) received increased plasma sodium concentrations in intravenous fluids. Forty-eight patients were tested (95% CI 30 to 116) for each such management change. Of the 23 patients with plasma sodium above 155 mmol/l, 21 (91.3%, 95% CI 72% to 98.9%) had a repeat plasma sodium measurement. Twenty-five patients were tested (95% CI 18 to 43) for each such management change.

5.5.2.2 Plasma potassium abnormalities

Management changes in patients with hypokalaemia are shown in Table 5.3. Fifty six percent of patients (95% CI 48.6 to 64.2) with plasma potassium levels below 3 mmol/l received additional potassium supplementation, and 82% (95% CI 66.5 to 92.5) with a level below 2 mmol/l received the required intravenous supplementation. The proportion of children receiving additional oral supplementation increased with decreasing potassium, as did intravenous supplementation.

Six patients needed to be tested for one patient to receive additional KCl orally for potassium levels of <3 mmol/l, 19 patients for a potassium level of <2 mmol/l and 44 for potassium levels of <1.5 mmol/l (Table 5.4). Sixteen patients needed testing for one to receive intravenous supplementation for a plasma potassium level below 2 mmol/l.

Two hundred and two patients (38.2%, 95% CI 34% to 42.2%) had either abnormal plasma sodium or abnormal plasma potassium or both. Three patients were tested (95% CI 2 to 3) for each electrolyte abnormality detected.

Table 5.3 Management of plasma potassium abnormalities – proportions of adherence to protocol

	Hypokalaemia			Severe hypokalaemia					
	<3			<2			<1.5*		
	%	of	95% CI	%	of	95% CI	%	of	95% CI
Oral KCl > 1.5 g per 24 hours	56.4	156	[48.6 to 64.2]	75.8	37	[58.8 to 88.2]	92.3	12	[64.0 to 99.8]
Additional KCl in intravenous fluids	-	-	-	82.1	39	[66.5 to 92.5]	92.3	12	[64.0 to 99.8]

*No patients had a potassium level <1.0 mmol/l.

Table 5.4 Number needed to test (NNT) to change management of one patient with plasma potassium abnormalities

	Hypokalaemia		Severe hypokalaemia			
	<3.0		<2.0		<1.5	
	NNT	95% CI	NNT	95% CI	NNT	95% CI
Oral KCL > 1.5g per 24 hours	6	[5 to 7]	19	[14 to 29]	44	[28 to 99]
Additional KCL in intravenous fluids	-	-	16	[12 to 25]	44	[28 to 99]

5.5.3 Sensitivity analyses

Two sensitivity analyses were performed (post hoc) to assess the difference that patients enrolled into the study, who were admitted the previous night, had on a) the proportion of management of electrolyte abnormalities according to protocol; and b) the number of patients that needed to be tested to change management the of one patient with an electrolyte abnormality.

a) Management of electrolyte abnormalities in accordance with protocol

Three patients had abnormal plasma sodium levels. Of these, one patient had a plasma sodium level below 125 mmol/l and received increased plasma sodium concentrations in the intravenous fluids. Two patients had plasma sodium levels above 155 mmol/l and had a repeat plasma sodium measurement. One patient had a plasma potassium level <3 mmol/l and received additional potassium supplementation. Exclusion of patients admitted after hours resulted in no meaningful changes in the proportion of patients that were managed according to protocol (Table 5.5).

b) Number needed to test to change management of one patient with an electrolyte abnormality

The number needed to test to change management of one patient with either a plasma sodium or plasma potassium abnormality was unchanged when children admitted after hours were excluded from the analysis (Table 5.6).

Table 5.5 Sensitivity analysis excluding patients admitted after hours – management of electrolyte abnormalities (proportions of adherence to protocol)

	Patients admitted during the day and overnight			Excluding patients admitted overnight		
	%	of	95% CI	%	of	95% CI
Plasma sodium <125 mmol/l and received additional plasma sodium in intravenous fluids	61.1	18	35.7 to 82.7	58.8	17	32.9 to 81.6
Plasma sodium > 155 mol/l and had a repeated plasma sodium measurement	91.3	23	72.0 to 98.9	90.5	21	69.6 to 98.8
Plasma potassium <3 mmol/l and oral KCL > 1.5g per 24 hours	56.4	156	48.6 to 64.2	56.1	155	48.3 to 63.9

Table 5.6 Sensitivity analysis excluding patients admitted after hours - number needed to test (NNT) to change management of one patient with electrolyte abnormalities

	Patients admitted during the day and overnight		Excluding patients admitted overnight	
	NNT	**95% CI**	**NNT**	**95% CI**
Plasma sodium <125 mmol/l and received additional plasma sodium in intravenous fluids	48	[30 to 116]	48	[31 to 128]
Plasma sodium > 155 mol/l and had a repeated plasma sodium measurement	25	[18 to 43]	25	[18 to 47]
Plasma potassium <3 mmol/l and oral KCL > 1.5g per 24 hours	6	[5 to 7]	6	[5 to 7]

5.6 Discussion

5.6.1 Interpretation of the principal findings

A fairly high proportion of patients were appropriately managed according to the treatment protocols. However, the number of patients that needed to be tested for each change in management was high, because of the relatively low prevalence of some abnormalities. An example of this is plasma potassium levels <1.5 mmol/l, with a prevalence of 2.5% and the number needed to test between 40 and 44 patients for any management change. This low prevalence also means that confidence intervals around many estimates were broad; for example, for potassium <1.5 mmol/l, 95% CI for number needed to test for any management change ranged between 29 and 99 patients. Even larger numbers (48 patients, 95% CI 30 to 116) were tested for one management change in the case of hyponatraemia (plasma sodium <125 mmol/l). For more prevalent and less severe conditions, for example, hypokalaemia (potassium <3 mmol/l), fewer patients (3 to 4) needed testing to identify one patient and to change management (5 to 7 patients).

Although a small number of patients were recruited into the study that were admitted overnight, a sensitivity analysis excluding these patients showed that inclusion of the patients did not bias the findings (Tables 5.5 and 5.6).

The current study has established that routine electrolyte testing does result in management change. However, the benefits derived from detecting each abnormality need to be weighted against the effort and costs involved in performing many tests to identify one case of such abnormality. The appropriateness of such testing (when available) will depend on the prevalence of the target conditions and the balance between the expected benefits of testing and the costs thereof, both in terms of the adverse affects (for example, the discomfort and risk to the patient) and the use of resources

(both material and staff) in a context where there are usually many competing priorities. All such judgements depend on assumptions about the benefits expected from changes in clinical management and will vary from setting to setting.

5.6.2 Comparison with past studies

Previous research performed in Holland (Tjon A Ten, 1999) reported that when abnormally low levels of electrolytes were identified by routine electrolyte tests, it seldom led to change in treatment. In Tjon A Ten's (1999) report 8 (3%) of the patients had serum sodium levels >150 mmol/l and 1 (0.4%) had a serum sodium level <130 mmol/l and 1 a serum potassium level < 3.0mmol/l. Only the 1 case with hypokalaemia had management changed and 265 patients needed to be tested for one such management change to occur. The current study had a higher prevalence of hypernatraemia (plasma sodium levels >150 mmol/l, 7%), hyponatraemia (plasma sodium levels <125 mmol/l, 3.4%) and hypokalaemia (potassium levels <3 mmol/l, 31.6%) than the Holland study. The patients in the current study were more dehydrated, with 62.3% of the patients ≥5% dehydrated compared to Tjon A Ten's (1999) study where only 27.9% were reported as dehydrated. The higher prevalence of electrolyte abnormalities in the current study is to be expected because of the greater severity of dehydration in the sample, and the finding of more frequent abnormalities in dehydrated patients in Tjon A Ten's (1999) study.

It is difficult to make a direct comparison between the two studies since a different spectrum of patients was studied (children were presumably not as sick or malnourished in the Dutch study). Even so, Tjon A Ten's (1999) study reported that knowledge of an electrolyte abnormality (obtained by routine electrolyte testing) resulted in changed management even though the estimate was not statistically significant.

5.6.3 Generalisability of the findings

The findings of this study have a generalisability limited to well-resourced teaching hospitals in middle-income countries. The therapeutic impact of routine electrolyte measures seen in this study would generally be greater than in some other settings since the research was performed in a protocol-driven practice. Routine testing could be useful in settings with a higher prevalence of plasma sodium and potassium disturbances in children with dehydrating diarrhoea.

5.6.4 Strengths of the research

The sample of patients in this study was broadly representative of children admitted to diarrhoeal rehydration units in metropolitan Cape Town. This increased the generalisability of the findings, since the sample included patients from both urban and peri-urban areas and informal settlements.

Examining the patients' folders to determine a change in management associated with electrolyte disturbances was done without the medical officers being informed of this aspect of the project, and often occurred more than 24 hours after admission. The medical officers were therefore unlikely to have managed the patients any differently than they would have in everyday practice.

The study was performed in a protocol-driven practice with clear policies determining what should happen and when. Changes in management as a result of an electrolyte abnormality could thus be identified relatively easily as new treatment in keeping with protocol management for that disorder.

5.6.5 Limitations of the research

Information was collected retrospectively from the patients' folders to ensure that the study was performed unobtrusively. It was therefore not possible to put measures in place to control for inaccurate reporting by medical officers.

The crude criteria used to assess management change could have missed other subtle changes that were not a part of the protocol but performed on the basis of clinical judgement. These would not have been detected or recorded by the principal investigator. Therefore, changes in management reported in this study could be an underestimation.

Changes in management depend on recognition of the abnormal result and consequent protocol-based action. The extent to which the protocols were implemented is not known. This information would have helped to determine the measured changes in management.

The study was conducted predominantly in children admitted during working hours, when staffing and supervision may have been greater. The findings may thus not be generalisable to after-hours conditions, in which case the findings would probably represent an over-estimate of the therapeutic impact of routine testing.

5.6.6 Implications for practice

The findings of this study suggest that routine testing, even if feasible, is unlikely to result in sufficient benefit to justify the use of considerable resources in most of the resource-constrained settings where diarrhoea is an important problem.

5.6.7 Implications for future research

A more valid and meaningful evaluation of the impact of routine testing on clinical outcome would require a randomised controlled trial of the effect of routine management on meaningful clinical outcomes. Such a trial would also quantify the size of any benefit and thereby enable a more informed comparison with competing priorities.

5.7 Conclusion

Routine testing resulted in the detection of plasma sodium and potassium abnormalities.

When abnormalities had a relatively low prevalence, large numbers of patients needed to be tested for each case of management change. The benefit of such testing needs to be weighed against the costs of performing many tests before one abnormality is identified and treated, taking into consideration other health priorities, financial constraints, limited facilities and staffing in most settings were dehydrating diarrhoea is prevalent.

A randomised controlled trial would provide a more valid and meaningful evaluation of the impact of routine testing on clinical outcomes.

CHAPTER SIX: SUMMARY AND RECOMMENDATIONS

6.1 Determinants of seasonal plasma sodium and potassium disturbances in childhood diarrhoea

6.1.1 Literature review

No studies were identified that reported on determinants of the seasonal fluctuations in plasma sodium and potassium disturbances.

6.1.2 Contribution of this research

The seasonal fluctuations in plasma sodium and potassium levels are partially explained by both enterotoxigenic *E. coli* and Cryptosporidium working together, with enterotoxigenic *E. coli* having the larger effect on plasma sodium and Cryptosporidium the larger effect on plasma potassium. These findings are a new contribution to the current body of research.

Previously described associations with other non-seasonal factors were confirmed in this study, that is: higher levels of plasma sodium with younger age, breast-feeding and living in a brick house; higher levels of plasma potassium with increased parental education and lower levels of plasma potassium with longer duration of diarrhoea.

6.1.3 Implications for practice/public health responses

The findings of this study are not sufficiently specific to suggest public health interventions that would target seasonal plasma sodium and potassium disturbances.

6.1.4 Implications for research

A study to identify determinants of the both enterotoxigenic *E. coli* and Cryptosporidium could inform public health interventions that target prevention of seasonal plasma sodium and potassium disturbances.

6.2 Utility of clinical signs in diagnosis of plasma sodium and potassium abnormalities in childhood diarrhoea

6.2.1 Literature review

No reported studies have been specifically designed to assess the diagnostic accuracy of clinical signs associated with plasma sodium and potassium abnormalities in childhood diarrhoea or any other condition in children.

6.2.2 Contribution of this research

This study makes an important contribution to health by providing an understanding of the utility of clinical signs in the detection of electrolyte abnormalities in children. It is novel, being the first systematic study of clinical signs used in the detection of clinically important electrolyte disturbances in an unquestionably important condition.

Clinical signs were generally not useful and showed poor reliability in actual practice. The consistent pattern of low accuracy across all tests does, however, indicate unhelpful accuracy. Even though there is uncertainty around the estimates of diagnostic accuracy for less prevalent conditions because of low statistical power, the most optimistic plausible levels of accuracy are not clinically meaningful, given the low prevalence of the target conditions.

The 'negative' findings in this study of the poor diagnostic accuracy of commonly used clinical signs further add to the importance of the findings, in that many of the signs assessed are currently, though misleading, used in everyday practice.

6.2.3 Implications for practice

No clinical signs (as defined in the study) were identified that were clinically useful in actual practice. Although meaningful diagnostic accuracy has not been excluded for all signs examined, none appears likely to be useful at the low prevalence of severe abnormalities in children with diarrhoea.

6.2.4 Implications for research

It is possible that clearer definitions of clinical signs could improve the reliability and validity of these signs. A study incorporating these features would be required to demonstrate this.

6.3 Therapeutic impact of routine electrolyte measurement in management of plasma sodium and potassium disturbances

6.3.1 Literature review

No studies have reported on the therapeutic impact of routine electrolyte testing in low- and middle-income countries, where dehydration and plasma sodium and potassium disturbances in children with diarrhoea are more prevalent and where resource constraints on routine testing are most marked. One study in Dutch children with mostly non-dehydrating diarrhoea reported a low prevalence of plasma sodium and potassium abnormalities (Tjon A Ten, 1999). Testing did not result in significant management change in their practice.

6.3.2 Contribution of this research

This is the first exploratory study to report on the therapeutic impact of routine electrolyte testing in a low- or middle-income country. Even though plasma sodium and potassium disturbances identified by routine testing resulted in changed management, large numbers of patients needed to be tested for each case detected and management change in abnormalities with a relatively low prevalence.

6.3.3 Implications for practice

The appropriateness of routine testing (when available) will depend on the prevalence of the target conditions and the balance between the expected benefits of testing and the costs, both in terms of the adverse affects (for example, discomfort and risk to the patient) and the use of resources in a context where there are usually many competing priorities. All such judgements depend on assumptions about the benefits expected from changes in clinical management.

6.3.4 Implications for future research

A more valid and meaningful evaluation of the impact of routine testing on clinical outcome would require a randomised controlled trial of the effect of routine management on clinically meaningful outcomes. Such a trial would also quantify the size of any benefit and thereby enable a more informed comparison with competing priorities.

6.4 Applicability and generalisability of the findings

The children studied were drawn predominantly from socially disadvantaged

areas of Cape Town (informal settlements) such as Khayelitsha, Nyanga and Guguletu, but included children from other urban and peri-urban areas in metropolitan Cape Town. The findings for all three studies are therefore applicable to a broad spectrum of patients aged between 6 weeks and 2 years.

Findings regarding the clinical identification of electrolyte disturbances and routine electrolyte testing as a management tool have limited generalisability to well-resourced teaching hospitals in middle-income countries with a similar prevalence of plasma sodium and potassium abnormalities.

REFERENCES

Adelman, R.D. & Solhung, M.J. 1996. Fluid and electrolyte treatment of specific disorders. In: Behrman, R.E., Kliegman, R.M. & Arvin, A.M. (eds.). *Nelson Textbook of Pediatr.* 15th Edition. Philadelphia: Saunders: 218.

Ahiadeke, C. 2000. Breast-feeding, diarrhoea and sanitation as components of infant and child health: a study of large scale survey data from Ghana and Nigeria. *J Biosoc.Sci.*, 32(1): 47-61.

Ahmed, I. & Agusto-Odutola, T.B. 1970. Hypernatraemia in diarrhoeal infants in Lagos. *Arch Dis Child.*, 45(239): 97-103.

Altman, D.G. 1991. *Practical statistics for medical research*. London: Chapman and Hall: 349, 406, 411.

American Academy of Pediatrics. 1994. Recognition of respiratory failure and shock. In: Chameides, L. & Hazinski M.F. (eds.). *Textbook of Pediatric Advanced Life Support*. Dallas: American Heart Association: 2-6.

Banajeh, S. M. & Hussein, R. F. 1999. The impact of breastfeeding on serum electrolytes in infants hospitalized with severe dehydrating diarrhoea in Yemen. *Ann Trop Paediatr.,* 19(4): 371-376.

Barkin, R. 1997. *Pediatric Emergency Medicine*. 2nd Edition. St Louis: Mosby. Cited in: Johns Hopkins. 2002. Serum electrolyte disturbances. In: Harrison, V.C., (ed.). *The Harriet Lane Handbook: A Manual for Pediatric House Officers*. 16th Edition. St Louis: Mosby: 241, 244.

Beatty, D.W., Mann, M.D., Heese, Hde. V. & Berger, G.M. 1974. Acute dehydrating gastro-enteritis in undernourished infants. The diagnosis and correction of electrolyte and metabolic abnormalities. *S Afr Med J.*, 48(37): 1563-1568.

Black, R.E. 1990. Epidemiology of travelers' diarrhea and relative importance of various pathogens. *Rev Infect Dis.*, 12: S73–S79.

Bossuyt, P.M., Reitsma, J.B., Bruns, D.E., Gatsonis, C.A., Glasziou, P.P., Irwig, L.M *et al.* 2003. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Clin Chem.*, 49(1): 7-18.

Bradshaw. D., Groenewald. P., Laubscher, R., Nannan, N., Nojilana, B., Norman, R *et al.* 2003a. Initial burden of disease estimates for South Africa. *S Afr Med J.*, 93(9): 682-688.

Bradshaw, D., Bourne, D. & Nannan, N. 2003b. What are the leading causes of death among South African children? MRC Policy Brief No 3. Cape Town: Medical Research Council.

Bruck, E. 1969. Seasonal incidence of hypertonic dehydration in diarrhea of infants. *Am J Dis Child.*, 118: 582-584.

Bruck, E., Abal, G. & Aceto, T. Jnr. 1968. Pathogenesis and pathophysiology of hypertonic dehydration with diarrhoea: a clinical study of 59 infants with observations of respiratory and renal water metabolism. *Am J Dis Child.*, 115: 122-144.

Caksen, H., Odabas, D., Sar, S., Celebi, V., Arslan, S., Kuru, M. & Abuhandan, M. 2001. Hyponatraemic dehydration: an analysis of 78 cases. *Int Urol Nephrol.*, 33(3): 445-448.

Chambers, T.L. & Steel, A.E. 1975. Concentrated milk feeds and their relation to hypernatraemic dehydration in infants. *Arch Dis Child.*, 50(8): 610-615.

Chatterjee, A., Mahalanabis, D., Jalan, K.N., Maitra, T. K., Agarwal, S.K., Dutta, B *et al.* 1978. Oral rehydration in infantile diarrhoea. Controlled trial of

a low sodium glucose electrolyte solution. *Arch Dis Child.*, 53(4): 284-289.

Chhabra, A., Patwari, A.K., Aneja, S., Chandra, J., Anand, V.K. & Ahluwalia, T.P. 1995. Neuromuscular manifestations of diarrhea related hypokalemia. *Indian Pediatr.*, 32(4): 409-415.

Cleary, T.G., Cleary, K.R., DuPont, H.L., El Malih, G.S., Kordy, M.I., Mohieldin, M.S *et al.* 1981. The relationship of oral rehydration solution to hypernatraemia in infantile diarrhea. *J Pediatr.*, 99(5): 739-741.

Department of Health. South Africa Demographic and Health Survey – 1998. Full Report [Online]. Available: http://www.doh.gov.za/facts/sadhs-f.html [2005, June 10].

DeYoung, V.R. & Diamond, E.F. 1960. Possibility of iatrogenic factors responsible for hypernatremia in dehydrated infants. *JAMA.*, 20(173): 1806-1808.

Essential Drugs Programme South Africa. 1998. Standard treatment guidelines and essential drugs list. *Paediatric Hospital Level.* Pretoria: Department of Health: 13-14.

Farthing, M. J. 1992. Hypernatraemia, acute diarrhoea, and oral rehydration therapy. *Lancet.*, 339(8798): 936.

Fayad, I.M., Hirschhorn, N., Abu-Zikry, M. & Kamel, M. 1992. Hypernatraemia surveillance during a national diarrhoeal diseases control project in Egypt. *Lancet.*, 339(8790): 389-393.

Finberg, L. 1986. Too little water has become too much. The changing epidemiology of water balance and convulsions in infant diarrhea. *Am J Dis Child.*, 140(6): 524.

Finberg, L. 1973. Hypernatraemic (hypertonic) dehydration in infants. *N Engl J Med.,* 289: 196-198.

Finberg, L. & Harrison, H.E. 1955. Hypernatremia in infants; an evaluation of the clinical and biochemical findings accompanying this state. *Pediatr.*, 16(1): 1-14.

Gibbs, M.A., Wolfson, A.B. & Tayal, V.S. 2002. Electrolyte Disturbances. In: Marx, J.A., Hockberger, R.S., Walls, R.M., Adams J., Barkin, R.M., Barsan, W.G., *et al.* (eds.). *Rosen's Emergency Medicine: Concepts and Clinical Practice*. 5th Edition. Philadelphia: Mosby: 1724,1727.

Guyatt, G.H. & Rennie, D. 2002. *Users' Guides to the Medical Literature. Essentials of Evidence-Based Clinical Practice*. The Evidence-Based Medicine Working Group. Chicago: American Medical Association Press: 425.

Haddow, J. E. & Cohen, D.L. 1974. Understanding and managing hypernatremic dehydration. *Pediatr Clin.North Am.*, 21 (2): 435-441.

Health Systems Trust. 2003. Health Statistics. Diarrhoea Incidence < 5 per 1000 for Cape Town (2000-2002) [On line]. Available: http://www.hst.org.za/healthstats/item.php?item_id=132&mode=data&header_type=84. [2005, May 30].

Hill, I. D., Mann, M. D. & Bowie, M. D. 1981, Hypernatraemic dehydration. A prospective study in children with diarrhoeal disease. *S Afr Med J.*, 59(14): 479-481.

Hoge, C.W., Shlim, D.R., Echeverria, P., Rajah, R., Herrmann, J.E. & Cross, J.H. 1996. Epidemiology of diarrhea among expatriate residents living in a highly endemic environment. *JAMA.*, 275: 533-538.

Household, K.C., Mann, M.N. & Bowie, M.D. 1988. Enteropathogens associated with acute infantile diarrhoea in Cape Town. *S Afr Med J.*, 73: 83-87.

Ironside, A.G., Tuxford, A.F. & Heyworth, B. 1970. A survey of infantile gastroenteritis. *Br Med J.*, 3(713): 20-24.

Islam, S.S. & Khan, M.J. 1986. Risk factors for diarrhoeal deaths: a case-control study at a diarrhoeal disease hospital in Bangladesh. *Int J Epidemiol.*, 15: 116-121.

Jacobs, S.I., Holzel, A., Wolman, B., Keen, J.H., Miller, V., Taylor, J. & Gross, R.J. 1970. Outbreak of infantile gastro-enteritis caused by *Escherichia coli* O114. *Arch Dis Child.*, 45(243): 656-663.

Jaeschke, R., Guyatt, G.H. & Lijmer, J. 2002. Part 1: The basics. Diagnostic tests. In: Guyatt, G., & Rennie, D. (eds.). Users' Guides to the Medical Literature. Essentials of Evidence-Based Clinical Practice. The Evidence-Based Medicine Working Group. Chicago: American Medical Association Press: 198-199, 203, 206.

Jiang, Z.D., Lowe, B., Verenkar, M.P., Ashley, D., Steffen, R., Tornieporth, N *et al.* 2002. Prevalence of enteric pathogens among international travelers with diarrhea acquired in Kenya (Mombasa), India (Goa), or Jamaica (Montego Bay). *J Infect Dis.*, 185: 497-502.

Johns Hopkins. 2002. Serum electrolyte disturbances. In: Harrison, V.C., (ed.). The Harriet Lane Handbook: A Manual for Pediatric *House Officers*. 16th Edition. St Louis: Mosby: 244

Kahigwa, E., Schellenberg, D., Schellenberg, J.A., Aponte, J.J., Alonso, P.L. & Menendez, C. 2002. Inter-observer variation in the assessment of clinical signs in sick Tanzanian children. *Trans R Soc Trop Med Hyg.*, 96(2): 162-166.

Karrar, Z.A. & Abdullah, M.A. 1981. Gastroenteritis among children in Riyadh: a prospective analysis of 254 hospital admissions. *Ann Trop Paediatr.*, 1(2): 119-122.

Kassel, H.R., Buchanan, N. & Moosa, G.M. 1970. The treatment of the dehydrated Bantu child. *S Afr Med J.*, 44(42): 1203-1206.

Kosek, M., Bern, C. & Guerrant, R.L. 2003. The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. *Bull World Health Organ.*, 81(3): 197-204.

Kuzemko, J. A. 1969. Gastro-enteritis in infancy. *Postgrad Med J.*, 45(529): 731-735.

Macaulay, D. & Blackhall, M.I. 1961. Hypernatraemic dehydration in infantile gastro-enteritis. *Arch Dis Child.*, 36: 543-550.

Mahalanabis, D., Faruque, A.S., Islam, A. & Hoque, S.S. 1996. Maternal education and family income as determinants of severe disease following acute diarrhoea in children: a case control study. *J Biosoc Sci.*, 28(2): 129-139.

Mehasi, A. I. & Murthy, K. 1990. Hypernatraemic dehydration in the Hail region of Saudi Arabia. *Ann Trop Paediatr.*, 10(3): 261-264.

Molla, A.M., Rahman, M., Sarker, S.A., Sack, D.A., Molla, A. 1981. Stool electrolyte content and purging rates in diarrhoea caused by rotavirus, enterotoxigenic E. coli, and V. cholerae in children. *J Pediatr.*, 98(5): 835-8.

Montgomery, M., Burke, K., Paredes, E., Zaidi, S. 1997. Measuring living standards with DHS data: Any reasons to worry?, mimeo. The Population Council. New York, NY.

Mrozowski, A. 1996. Disorders of glucose metabolism. In: Strange, G.R., Ahrens, W., Lelyveld, S. & Schafermeyer, R. (eds.). *Pediatric Emergency Medicine*. New York: Mcgraw-Hill: 322.

Murray, C.J. & Lopez, A.D. 1997a. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet.*, 349(9061): 1269-1276.

Murray, C.J. & Lopez, A.D. 1997b. Global mortality, disability and the contribution of risk factors: Global Burden of Disease Study. *Lancet.*, 349(9063): 1436-1442.

Nathoo, K.J., Glyn-Jones, R. & Nhembe, M. 1987. Serum electrolytes in children admitted with diarrhoeal dehydration managed with simple salt and sugar solution. *Cent Afr J Med.*, 33(8): 200-204.

Paneth, N. 1980. Hypernatraemic dehydration of infancy: an epidemiologic review. *Am J Dis Child.*, 134(8): 785-792.

Pavia, A.T. 2004. Diarrhea and food borne Illness. In: Cohen, J., Powderly, W.G., Berkley, S.F., Calandra, T., Clumeck, N., Finch, R.G, *et al.* (eds.) *Infectious Disease*. 2nd Edition. St Louis: Mosby: 1446, 1448.

Pickering, L.K. & Snyder J.D. 2004. Gastroenteritis. In: Behrman, R.E., Kliegman, R.M. & Jenson, H.B. (eds.). *Nelson Textbook of Pediatrics*. 17th Edition. Philadelphia: Saunders: 1274.

Prinsloo, J.G. & Kruger, H. 1970. Electrolyte and nutrition status of Bantu children with gastro-enteritis. *S Afr Med J.*, 44(17): 491-493.

Provincial Administration of the Western Cape. 1995. *Provincial Plan.* Cape Town: Provincial Administration of the Western Cape/PAWC.

Puffer, R.R. & Serrano, C.V. 1973. *Patterns of Mortality in Childhood: Report of the Inter-American Investigation of Mortality in Childhood.* Scientific Publication No. 262. Washington DC: Pan-American Health Organisation.

Purohit, K.R. & Jyotsna, P.S.R. 1971. Electrolyte disturbances in acute diarrhoea. *Indian J Pediatr.*, 38: 393-395.

Qadri, F., Das, S.K., Faruque, A.S., Fuchs, G.J., Albert, M.J., Sack, R.B. & Svennerholm, A.M. 2000. Prevalence of toxin types and colonization factors in enterotoxigenic *Escherichia coli* isolated during a 2-year period from diarrheal patients in Bangladesh. *J Clin Microbiol.*, 38(1): 27-31.

Raghu, M.B., Deshpande, A. & Chintu, C. 1981. Oral rehydration for diarrhoeal disease in children. *Trans R Soc Trop Med Hyg.*, 75(4): 552-555.

Royal College of Paediatrics and Child Health. 2000. Guidelines for the ethical conduct of medical research involving children. *Arch Dis Child.*, 82:177-182.

Rosenfeld, W., de Romana, G.L., Kleinman, R. & Finberg, L. 1977. Improving the clinical management of hypernatremic dehydration. Observations from a study of 67 infants with this disorder. *Clin Pediatr (Phila).*, 16(5): 411-417.

Rudzinski, J.P., Wolanyk, D. & Mackey, M. 1996. Fluid and electrolytes. In: Strange, G.R., Ahrens, W., Lelyveld, S. & Schafermeyer, R. (eds.). *Pediatric Emergency Medicine*. New York: Mcgraw-Hill: 342, 346.

Sackett, D.L., Haynes, R.B., Guyatt, G.H. & Tugwell, P. 1991. *Clinical epidemiology. A Basic Science for Clinical Medicine.* 2nd Edition. Boston: Little Brown and Company: 19, 30, 55, 91, 120, 131.

Samadi, A. R., Wahed, M. A., Islam, M. R. & Ahmed, S. M. 1983. Consequences of hyponatraemia and hypernatraemia in children with acute

diarrhoea in Bangladesh. *Br Med J (Clin Res Ed).*, 286(6366): 671-673.

Simel, D.L., Samsa, G.P. & Matchar, D.B. 1991. Likelihood ratios with confidence: sample size estimation for diagnostic test studies. *J Clin Epidemiol.*, 44(8): 763-770.

Skinner, A.L. & Moll, F.C. 1956. Hypernatremia accompanying infant diarrhea. *Am J Dis Child.*, 92(6): 562-575.

Swingler, G.H. 2004. Normal values and useful information. In: Harrison, V.C. (ed.). *Handbook of Paediatrics in Developing Countries*. 6th Edition. Cape Town: Oxford University Press: 481.

Swingler, G.H. & Power, D. 2002. Seasonal plasma electrolyte fluctuations in childhood diarrhoea. *Arch Dis Child.*, 87(5): 426-427.

Taylor, D.N., Houston, R., Shlim, D.R., Bhaibulaya, M., Ungar, B.L. & Echeverria, P. 1988. Etiology of diarrhea among travelers and foreign residents in Nepal. *JAMA.*, 260: 1245-1248.

Thapar, N. & Sanderson, I.R. 2004. Diarrhea in children: an interface between developing and developed countries. *Lancet.*, 363(9409): 641-653.

Tjon A Ten, W.E. 1999. [Children hospitalized with acute gastro-enteritis. Electrolyte imbalances seen primarily in clinical dehydration]. *Ned Tijdschr Geneeskd.*, 143(6): 303-305.

Travis, L.B. 1996. Disorders of water, electrolyte and acid-base physiology. In: Rudolph, A.M., Hoffman, J.I.E. & Rudolph, C.D. (eds.). *Rudolph's Pediatrics*. 20th Edition. Stanford: Appleton & Lange: 1331.

United Nations Children's Funds. 2002. *The State of the World's Children 2002*. New York: UNICEF.

Weil, W. & Wallace, W. 1956. Hypertonic dehydration in infancy *Pediatr.*, 17(2): 171-183.

Woodward, W.E. & Woodward, T.E. 1986. Management of dehydrating diarrhea. *Hosp Pract (Off Ed).*, 21(3A): 60, 63, 67-70.

World Medical Association. 2000. World Medical Association Declaration of Helinski. Ethical principles for medical research involving human subjects. 52nd WMA General Assembly, Edinburgh, Scotland.

World Health Organization. 2000. *World Health Report 2000 Global Water Supply* and Sanitation Assessment [On line]. Available: http://www.who.int/water_sanitation_health/diseases/diarrhoea/en/ [2005, May 18].

Yousuf, A., Fayyad, I.M. & Ebrahim, G.J. 1988. The clinical epidemiology of hypernatraemia in diarrhoea during treatment with oral rehydration in Egypt. *J Trop Paediatr.*, 34: 289-293.

Zaman, K., Islam, M.R., Baqui, A.H. & Yunus, M. 1985. Hypokalaemia in children with diarrhoea in rural Bangladesh. *Indian J Med Res.*, 81: 169-174.

APPENDICES: CHAPTER TWO

E

Appendix 2.1 Consent form for study of electrolyte levels in childhood diarrhoea

Description of the study

The levels of salt in the blood of children with diarrhoea can sometimes be abnormal. To treat these abnormal levels we need to know more about what causes them and how to check for the abnormalities. The purpose of this research study is to try to understand 1) what things influence the levels of salts in the blood of children with diarrhoea and 2) the best way to check for abnormalities of the levels of salts in the blood when examining children with diarrhoea.

In this study we will collect information by asking questions, doing laboratory tests and examining the children's folders for information about how they were treated. We will not change any treatment. We will be doing tests on some of baby's stool / blood. The nurse will be taking some stool from baby's nappy / The doctor will be taking blood from baby. We need to study 700 children in order to get reliable results.

What this means for you and your child is that:

1. We would ask you questions about baby's illness and what baby eats.
2. We would ask you a few questions about your schooling, where you live and family income.
3. We would take blood from your child to measure the levels of salt in the blood. This is usually done as a part of the child's ordinary care, even if he/she is not in the study.
4. We would collect a specimen of stool from your child's nappy and send it to the laboratory to test for germs that may be causing the diarrhoea, and for salt levels.
5. Your child's treatment will not be changed in any way.
6. The results of this study will be presented at medical conferences and in articles in medical journals, but in such a way that it will be impossible to identify your child individually.
7. Taking part in this study is completely voluntary and you may withdraw at any time without giving an explanation.
8. Your child's care will not be affected if you do not agree to take part or if you withdraw from the study.
9. We may store some stool to be tested at a later stage for any other germs.

I_____ the mother/father/guardian of

_____verify that;

1. I understand the information that has been given to me.
2. The information is in the language of my choice, or through an interpreter.
3. I have been given a chance to ask questions.
4. I may consult with family and friends before agreeing to take part.
5. I have a copy of this consent form, with the researcher's contact information.

_____ _____ _____

Person giving consent Researcher Witness

Date:_____

Victoria Pillay, Red Cross Hospital, Dept of Paediatrics and Child Health, Ph: 021 658 5120

A

Appendix 2.2 Toestemmingsvorm vir deelname aan navorsingstudie oor elektrolise-vlakke in kinders met diaree

Beskrywing van navorsingstudie

Die soutvlakke in die bloed van kinders met diaree is soms abnormaal. Ten einde hierdie abnormale soutvlakke te behandel, is dit nodig om te weet wat die oorsaak is van hierdie afwyking en hoe om te toets vir hierdie abnormaliteite. Die doel van hierdie navorsingstudie is om te bepaal wat 1) die faktore is wat bloedsoutvlakke in kinders met diaree beïnvloed en 2) die bes moontlike wyse(s) om te toets vir abnormaliteite in bloedsoutvlakke in kinders met diaree wanneer hulle ondersoek word.

In hierdie studie wil ons inligting insamel deur vrae te vra, laboratoriumtoetse te doen en die kinders se lêers te inspekteur (om uit te vind hoe hulle behandel is). Ons sal nie afwyk van die roetine behandeling wat baba moet ontvang nie. Toetse sal gedoen word op baba se stool gang bloedmonster. Die verpleegster sal verantwoordelik wees om stool gang van baba se doek te neem / Die dokter sal bloedmonsters van baba neem. Ons benodig 700 kinders om deel te neem aan die navorsingstudie om betroubare resultate te kry.

Vir u en u kind beteken dit dat:

1. Ons sal vir u vrae vra oor die baba se siekte en eetgewoontes.
2. Ons sal vir u 'n paar persoonlike vrae vra oor u opleiding, waar u woon en u huishouding.
3. Ons sal bloedmonsters neem van u kind ten einde bloedsoutvlakke te meet. Dit is deel van roetine behandeling vir alle kinders met diaree, ongeag of hy/sy in die studie is of nie.
4. Ons sal 'n stool gang van 'n baba se doek neem en laboratoriumtoetse doen om soutvlakke te meet en agente (kieme) wat diaree veroorsaak te identifiseer.
5. Daar sal nie afgewyk word van die roetine behandeling wat u kind ontvang nie.
6. Die resultate van die navorsing sal voorgelê word by mediese kongresse en gepubliseer word in mediese tydskrifte, maar die identiteit van 'n kind sal nie bekend gemaak word nie.
7. Deelname aan hierdie studie is vrywillig, en u mag enige tyd onttrek sonder dat dit nodig is vir 'n verduideliking.
8. U kind se sorg sal nie beïnvloed word indien u besluit om nie deel te neem aan hierdie studie, of deelneem en later onttrek van die studie nie.
9. Ons mag stool gang oorhou om op 'n later stadium te toets vir enige ander kieme.

Ek_____ die moeder/vader/voog van

_____verklaar dat;

1. Ek verstaan die inligting wat vir my gegee is,
2. Die inligting verskaf is in 'n taal van my keuse, of deur 'n tolk,
3. Ek is 'n kans gegun om vrae te vra oor ander aspekte waaroor ek onduidelik is,
4. Ek mag my gesin en vriende raadpleeg voor ek toestemming gee aangaande deelname aan die studie.
5. Ek het 'n afskrif van hierdie toestemmingvorm met die navorser se kontak besonderhede.

_____	_____	_____
Persoon wat toestemming gee	Navorser	Getuenis

Datum:_____

Victoria Pillay, Red Cross Children's Hospital, Dept of Paediatrics and Child Health, Ph: 021 658 5120

Appendix 2.3 Isiqinisekiso sesivumelwano ngophando lwemilinganiselo yeetyuwa kwintsana ezino-Rhudo

Inkcazelo ebanzi ngophando
Umlinganiselo wetyuwa esegazini kubantwana abane sifo sorhudo maxa wambi sibenza babe buthathaka. Ukunyanga le milinganiselo kufuneka sazi ngokubanzi ukuba kwenziwa, kwaye iyintoni ebangela olo xinzeleleko. Isizathu sokwenza olu phando kukufuna ukuqonda 1) Ingaba zintoni ezibanga lemilinganiselo yetyuwa esegazini labantwana abanesifo so rhudo, 2) Eyona ndlela yokukhangela olu xinzeleleko lwale milinganiselo yetyuwa esegazini xa kuxilongwa abantwana abanorhudo.

Kolu phando lwezizifundo sakuthi siqokelele ulwazi ngokuthi sibuze imibuzo, ngokusebenzisa uphando kunye noxilongo gazi kwifolda zabantwana ukufumana inkcazelo engakumbi ukuba luluphi unyango abathe balufumana. Asiyi kuyitshintsha indlela yonyango abathe balufumana. Sobe sisenza uphando kugutyulo lwelindle okanye kwigazi. Umongikazi wothabatha inxalenye yogutyulo olufumaneka esishubeni somntwana, yena ugqirha watsala igazi emtwaneni lowo. Sifuna ukwenza uphando ukuyakufika kuma 700 abantwana ukwenzela sifumane ezona ziphumo zigqibeleleyo ngolu phando.

Ingaba kuthetha ukuthini oku kuwe kunye nontwana,

1. Sakuthi sibuze imibuzo ngokuphathelele ukugula komntwana kwakunye nokutya akutyayo.
2. Sakuthi sibuze imibuzo embalwa ngemfundo yakho, ukuba uhlalaphi kwaye usebenzisa malini nyanga nganye.
3. Sakuthi sithabathe igazi emntwaneni wakho ukuze sikhangele umlinganiselo wetyuwa esegazini.Oku kuvame ukwenzeka njengenxalenye yonyango ingekuba uzele uphando.
4. Sakuthi sithabathe inxenye yogutyulo oluphuma kwishuba somtwana, esakuthi sisithumele kwigumbi lophando zintsholongwane ezibangela urhudo kwakunye nemilinganiso yetyuwa egazini.
5. Unyango lomntwana wakho aluyi kutshintsha nangayiph' indlela.
6. Iziphumo zolu phando zonikezelwa kwinkongolo yezonyango kwakunye nezicatshulwa zonyango, oku kuya kuthi kubenzima ukuveza ukuba ngubani na lowo kuphandwa ngaye.
7. Ukuthabatha inxaxheba kolu phando kokokuzithandela akusosiso isinyanzelo, kwaye unokurhoxa nagaliphi ixesha ufuna kungekhona nankcazelo.
8. Inkathalo engontwana wakho ayisayi kuphazamiseka kuba ungafuni kuthabatha inxaxheba okanye ukurhoxa koluphando.
9. Sinako ukugcina inxalenye yogutyulo ukwenzela ukuphanda kwakhona kwixesha elizayo malunga nentsholongwane ezikulo.

Mna _____Mama/Tata/Mgcini ka

_____ndivumelana nokuba

1. Ndiyaqonda ngenkcazelo endiyixelelweyo.
2. Lenkcazelo ingolwimi lwam lwentando, nangoku phuhliswa yitoliki.
3. Ndilinikiwe ithuba lokubuza imibuzo.
4. Ndinako ukunxulumana nosapho okanye izizalwana phambi kokwenza isigqibo sokuthabatha inxaxheba.
5. Ndinaso isiqinisekiso sesivumelwano esinenkcazelo ngomphandi wemfunalwazi.

_____	_____	_____
Umzali	Umphandi	Itoliki

Umhla:_____

Victoria Pillay, Red Cross Children's Hospital, Dept of Paediatrics and Child Health, Ph: 021 658 5120

Appendix 2.4 Ethical approval for research from the Research Ethics Committee

UNIVERSITY OF CAPE TOWN

Research Ethics Committee
Faculty of Medicine
Anzio Road, Observatory, 7925
Queries : Martha Jacobs
Tel : (021) 406-6492 Fax: (021) 406-6390
E-mail : Martha@medicine.uct.ac.za

03 May 2000

REC REF: 097/2000

Dr G Swingler
Paediatrics
Red Cross Hospital

Dear Dr Swingler

ELECTROLYTE DISTURBANCES IN CHILDHOOD DIARRHOEA

Thank you for your application submitted to the Research Ethics Committee on 31 March 1999.

I have pleasure in informing you that the Research Ethics Committee has **formally approved** the above study on 02 May 2000.

You may proceed with the trial once the financial agreement/contract and protocol have been processed through the department of Research Development and duly signed by the authorised University of Cape Town signatories.

Included is a list of Research Ethics Committee Members who have formally approved your protocol.

Please quote the above Reference number in all correspondence.

Yours sincerely,

PROFESSOR DM DENT
ACTING-CHAIRPERSON

Queries: Martha Jacobs
Research Ethics Committee
Room 212 Werner and Beit
UCT Medical School
Anzio Road, Observatory, 7925
Tel: (021) 406-6492 Fax: (021) 406-6390

APPENDICES: CHAPTER THREE

Appendix 3.1 PubMed search strategy for determinants of electrolyte disturbances: period 1966 to May 2005

#1 Search Diarrhea

#2 Search Diarrhoea

#4 Search "Diarrhea"[MeSH]

#5 Search "Hyponatremia"[MeSH]

#6 Search "Hypernatremia"[MeSH]

#7 Search "Hyperkalemia"[MeSH]

#8 Search "Hypokalemia"[MeSH]

#9 Search "Potassium/blood"[MeSH]

#10 Search "Sodium/blood"[MeSH]

#11 Search #1 OR #2 OR #4

#12 Search #5 OR #6 OR #7 OR #8 OR #9 OR #10

#13 Search "Causality"[MESH]

#14 Search "Hyponatremia/etiology"[MESH]

#15 Search "Hypernatremia/etiology"[MESH]

#16 Search "Hyperkalemia/etiology"[MESH]

#17 Search "Hypokalemia/etiology"[MESH]

#18 Search #11 AND #12 AND #13

#19 Search #14 OR #15 OR #16 OR #17

#20 Search #11 AND #19

#21 Search #18 OR #20 Limits: Humans

Appendix 3.2 Gastro Electrolyte Study: LABORATORY RESULTS ON ☐

Name:_____

Folder No:_____

D.O.B:_____ R/S:__

Date of admission: ___/__/_____

Biochemistry

Plasma Na^+: _____ K^+: _____

pH: _____

Microbiology

Stool collected **Y / N**

If no reason _____

	Y	N
No growth		
Shigella		
Salmonella		
Campylobacter		
Cryptosporidium		
Rotavirus		
Enteropathogenic *E. coli*		
Enterotoxigenic *E. coli*		
Enteroaggregative *E. coli*		
Enterohaemorrhagic *E. coli*		
> than one *E. coli* type		

E

Appendix 3.3 Gastro Electrolyte Study: BASELINE DEMOGRAPHIC QUESTIONNAIRE

Date of admission: ___/_____/_____ Time:_____

Folder No:_____

Name:_____

DOB:_____/___/_____ R/S:_____

Eligibility

Ma'am, how old is Baby?_____months

Were you sent here from another hospital or ward? **Y / N**

Has baby been in a research study with me before? **Y / N**

Is baby on diuretics? **Y / N**

History

Can you please tell me the following things about baby's illness

How long has baby been sick with diarrhoea?_____Day(s)

Has baby been vomiting? **Y / N**

If yes

For how long:_____Day(s)

Is baby drinking as well as s/he usually does: **Y / N**

If no

Less than usual ☐

Not at all ☐

How many times has baby had diarrhoea in the past three months where baby needed to be taken to a doctor?_____

Has baby had fits in the last 24 hours? **Y / N**

Has baby been crying more than usual? **Y / N**

If yes

Crying but you can calm baby ☐

Crying but cannot calm baby ☐

Diet

Ma'am, can you please tell me the following things about baby's feeding habits.

Is baby on the breast only? **Y / N**

If no

Is baby bottle-fed? **Y / N**

Which bottle feed? _____

E

Is baby on solids? _____ Y / N

Does baby drink any thing else? Y / N

If yes could you tell me what

_____

Treatment before admission

Ma'am I am now going to ask a few questions about how you have been treating the diarrhoea before you came here today.

Have you needed to visit anybody for treatment of baby's diarrhoea before coming the to RCCH? Y / N

'Traditional' /Pharmacist /Clinic nurse / Clinic doctor / GP

Have you been giving baby anything to drink as treatment for the diarrhoea ? Y / N

If yes, what did you give baby?

☐ Sachet: _____

☐ Salt and sugar solution: _____

☐ Other: _____

How did you make it?

_____

_____

What liquid did you use and how much? _____ ml

No. spoons salt: _____

No. spoons sugar: _____

Ma'am could you please show me from all the spoons in the box which size spoon you used.

A B C

Other treatments

Have you been giving baby anything else to treat the diarrhoea? Y / N

If yes describe

_____

E

Ma'am I am now going to ask a few questions about yourself and where you live.

What is the highest education level you have reached?

No education ☐

School (Std / Grade):_____

Tertiary education passed

Training college (no of years):_____ ☐

Technikon (no of years):_____ ☐

University (no of years):_____ ☐

Other:_____ ☐

In what type of house do you live in?

House on a separate site ☐

Hut/traditional house ☐

Flat in a block of flats ☐

Semi-detached/cluster/town house ☐

House or a flat in the backyard ☐

Shack in the backyard ☐

Shack not in the backyard ☐

Room in a hostel or compound provided for you by your boss ☐

Other:_____ ☐

Please tell me whether you and your family have access to the following

Chemical toilet ☐

Pit latrine ☐

Bucket toilet ☐

None ☐

	In house	On site	Off site
Flush toilet	☐	☐	☐
Water source	☐	☐	☐

E

Family income

Please tell me which of the following things you have in the house and whether they are working or not.

	Y	N	Yes but not working (explain)
Electricity	1	2	3 _____
Stove (electric,gas, coal, wood, paraffin [primus])	1	2	3_____
Other:_____			
Refrigerator/ deepfreeze	1	2	3_____

Recent urbanisation

Where do you live? _____

When did you move into this area?_____

Has baby always lived here? **Y/ N**

During the past year has baby lived somewhere else for any period? **Y/ N**

With whom and for how long (> than 1 month):_____

Where:_____

A

Appendix 3.4 Gastro Electrolyte Study: BASELINE DEMOGRAPHIC QUESTIONNAIRE

Toelatingsdatum:_____/_____/_____ Tyd: _____

Leêr No:_____

Naam:_____

D.O.B:_/__/____ R/S:_____

Toelatingskriteria

Hoe oud is Baba:_____maande

Is dame na hierdie hospitaal verwys deur 'n ander hospitaal of 'n ander saal in hierdie hospitaal? **J / N**

Het dame al vantevore 'n vraelys by *my* ingevul oor *hierdie* baba? **J / N**

Drink baba medisyne vir die hart? **J / N**

Geskiedenis
Kan dame vir my asseblief meer vertel oor u baba se siekte?

Hoe lank het die baba diarree ("loop magie")? _____Dag(e)

Vomeer die baba (gooi op)? **J / N**

Indien ja,

Hoe lank gebeur dit al?_____Dag(e)

Drink die baba soos gewoontlik? **J / N**

Indien nee,

Minder as gewoontlik? ☐

Glad nie? ☐

Behalwe hierdie keer, hoeveel keer gedurende die afgelope drie maande moes baba mediese sorg kry vir diaree? _____

Oor die afgelope 24 uur, het baba enige stuipe gekry? **J / N**

Huil baba meer as gewoontlik? **J / N**

Indien ja,

Kan baba kalmeer. ☐

Kan nie baba kalmeer nie. ☐

A

Dieet

Kan dame vir my asseblief meer vertel oor baba se eetgewoontes:

Drink baba net borsmelk? (en geen ander formule ["poeier"] melk nie) **J / N**

Indien nee,
Kry baba formule ["poeier"] melk? **J / N**

Watter forumule melk gebruik baba ? _____

Eet baba vaste stowwe?_____J / N

Drink baba enigiets anders? (*Koffie, tee, Coke, ens.)*

Indien ja, kan jy vir my sê wat?

_____

Behandeling voor toelating
Kan dame vir my meervertel oor hoe u baba se diarree behandel het voor u na die hospitaal gekom het:

Het u enige iemand besoek om baba se diarree te behandel
voor u na die RKKH gekom het? **J / N**

Indien ja, wie?

Traditionele' /Apteek /Klinieksuster/Kliniekdokter / Huisdokter

Het u vir baba enigiets gegee om te drink om die diaree te behandel? **J / N**

Indien 'Ja', wat ?

- ☐ Sakkie (van apteek):_____
- ☐ Sout en suiker oplossing:_____
- ☐ Ander:_____

Hoe het u die oplossing gemaak?

_____

_____

Met watter vloeistof het u die oplossing gemeng?_____

Hoeveel vloeistof het u gebruik? _____ml/koppies

Aantal lepels sout:_____

Aantal lepels suiker:_____

A

Dame, kan u asseblief vir my wys watter grootte lepel u gebruik het om die oplossing aan te maak?

A B C

Ander behandeling

Het u enigiets anders vir baba gegee om die diaree te behandel? **J / N**

Indien ja, beskryf:

_____

Dame, kan ek vir u 'n paar vrae vra oor u self en waar u woon?

Vir hoeveel jaar was dame al by die skool?

Ongeskoold ☐

Skool (St / Graad geslaag):_____ ☐

Het dame na skool verder studie? **J / N**

Indien ja

Waar en vir hoe lank?

Tertiêre opleiding voltooi

Opleidingskollege (aantal jare):_____ ☐

Technikon (aantal jare):_____ ☐

Universiteit (aantal jare):_____ ☐

Ander:_____ ☐

In watter tipe huis woon dame?

Alleenstaande huis ☐

Hut/rondawel (traditionele huisstruktuur) ☐

Woonstel in woonstelblok ☐

Skakel/dorpshuis ☐

Huis/ woonstel /kamer in agterplaas ☐

Plakkershuis in agterplaas ☐

Plakkershuis nie in agterplaas ☐

Kamer in koshuis of woonkwartier voorsien deur werkgewer ☐

Ander:_____ ☐

A

Het u en u familie toegang tot die volgende fasiliteite:

Chemiese toilet ☐

Gat in grond ☐

Emmer gebruik as toilet ☐

Geen ☐

	In Huis	Op erf	Buite erf
Spoel toilet	☐	☐	☐
Water bron	☐	☐	☐

Familie inkomste

Kan dame asseblief vir my aandui of u die volgende items besit in u huis ongeag of dit werk of nie:

	J	**N**	**Ja, maar werk nie.** (verduidelik)
Elektrisiteit	1	2	3 _____
Stoof (elektries, gas, steenkool, hout, paraffien [primus])	1	2	3_____
Ander:_____			
Yskas/vrieskas	1	2	3_____

Waar woon u?_____

Hoe lank woon u in hierdie area: _____

Hoe lank woon u in hierdie huis: _____

Woon baba sy/haar van geboorte af hier? **J / N**

Indien nee

Met wie / waar het baba tevore gebly: _____

Vir hoe lank? _____

Het baba gedurende die afgelope jaar êrens elders gewoon vir enige tyd **J / N**

Indien ja, met wie (> 1 maand):_____

Vir hoe lank?_____

Waar:_____

Appendix 3.5 Methods used to identify enteropathogens – provided by Andrew Whitehead and Karen Mcabe of the Institute of Child Health, Red Cross Children's Hospital, 2003

Salmonella / Shigella / Campylobacter culture (AW):

Stool samples were emulsified in normal saline (if necessary) and inoculated onto SS (Salmonella/Shigella) agar plates (McC [McConkey] agar plates) and into buffered peptone water.

Campylobacters were isolated by placing a drop of emulsified stool on a 6 um filter on a tryptose blood agar (TBA) plate for 15 minutes. The filter was then removed and the TBA plate incubated at 35°C in appropriate atmospheric conditions (in an anaerobic jar with a BR 38 sachet). The TBA plates were examined every 48 hours for 6 days. Colonies suspected of being Campylobacter species on the basis of Gram stain appearance and colony morphology were further identified as described below.

SS agar plates and McConkey agar plates were incubated overnight at 35°C aerobically and examined at 24 and 48 hours' incubation. Non-lactose- fermenting colonies were further identified as described below.

Buffered peptone water was incubated overnight at 42°C and subcultured onto MSRV (modified semi-solid Rappaport-Vassiliadis) agar after 24 hours. MSRV agar was then incubated at 35°C aerobically for 24 hours. Colonies that showed a "halo" on the agar were identified further.

The identity of non-lactose-fermenting colonies on the SS or McC agar plates were confirmed by means of standard biochemical reactions. Similarly, suspicious colonies on the MSRV agar were also identified:

- Fermentation of glucose, inositol and arabinose
- Indole production from tryptophane
- Presence of ornithine and lysine decarboxylase
- Production of urease
- Production of H_2S
- Growth on Simmon's citrate medium

- Presence of B galactosidase (ONPG)
- Motility
- Oxidase production

On the basis of these biochemical reactions, potential Salmonella and Shigella isolates were confirmed as such by means of agglutination reactions. Potential Shigella isolates were first agglutinated with specific *S. flexneri* antiserum (Mast Diagnostics). If this was negative, the isolate was typed using the Wellcolex Colour Shigella kit (Remel). Potential Salmonella isolates were typed using the Wellcolex Colour Salmonella kit (Remel).

Campylobacter isolates were identified by means of the following tests:

- Oxidase production
- Hippurate hydrolysis
- Indoxyl acetate hydrolysis
- Growth on McConkey agar
- H_2S production
- Susceptibility to nalidixic acid and cephalothin.

Microscopy for Cryptosporidium (AW):

Stool was emulsified in Sheather's Sugar Solution (500 g sucrose, 320 ml water, 6,5 g phenol) and examined under 400x magnification using a phase contrast filter. *C. parvum* oocysts were identified as refractile, round objects floating within the sugar solution, just below the cover-slip.

Latex agglutination for rotavirus (AW):

The presence of rotavirus was determined by using the Murex Rotavirus Latex kit (Murex) according to the manufacturer's instructions. Briefly, stool was added to the extraction buffer, vortexed and then centrifuged for 10 minutes. Test latex was added to one drop of supernatant, control latex to another drop of supernatant and mixed for up to 2 minutes. The presence of agglutination in the test latex (with no agglutination in the control latex) was taken as indicating the presence of rotavirus in the sample.

***E. coli* culture, isolation and identification (KM):**

Stool samples (four *E. coli* colonies/sample were sub-cultured) were cultured overnight on McConkey agar. Biochemical identification of the four *E. coli* isolates was done by sugar fermentation reactions using the Analytical Profile Index of *Enterobacteriaceae* (API 20E) system (Biomerieux). Serogrouping of E. coli isolates were done by slide agglutination tests using antisera specific for *E. coli* (Murex Biotech Ltd.). Isolates were stored on Microbank^{TM} vials (Pro-Lab Diagnostics) at -70^{0}C . Identification of the adherence patterns on the isolates was done by an *in vitro* adherence assay using HeLa cells. LT toxin (heat labile) production was detected by Reverse Passive Latex Agglutination using the VET-RPLA "SEIKEN" (Vibrio cholera and *E. coli* enterotoxins) kit (Denka Seiken Co., Ltd.). VT1 and VT2 (verotoxin 1 and verotoxin2) production was detected by Reverse Passive Latex Agglutination using the VTEC-Screen "SEIKEN" (*E. coli* verotoxins) kit (Denka Seiken Co., Ltd.). STh (heat stable toxin of human origin) coding genes were detected by a DNA hybridisation assay using digoxigenin-11-ddUTP (2',3'-dideoxyuridine-5'-triphosphate coupled to digoxigenin via an 11-atom spacer arm) labelled oligonucleotide probe and a chemiluminescent detection with CSPD (Roche Diagostics) (a commercial reagent which contains chemiluminescent alkaline phosphatase substrates), STp (heat-stable toxin of porcine origin) coding genes were detected by DNA hybridisation assay using a digoxigenin-11-ddUTP labelled oligonucleotide probe and a chemiluminescent detection with CSPD (Roche Diagnostics).

APPENDICES: CHAPTER FOUR

Appendix 4.1a PubMed search strategy for determinants of seasonal fluctuations in sodium and potassium levels in children less than 2 years old with diarrhoea: period 1966 to April 2005

#1 Search Hyponatremia

#4 Search Hypernatremia

#7 Search "Hyponatremia"[MESH]

#8 Search "Hypernatremia"[MESH]

#9 Search Hypokalemia

#10 Search Hyperkalemia

#11 Search "Hyperkalemia"[MESH]

#12 Search "Hypokalemia"[MESH

#13 Search #1 OR #4 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12

#16 Search (hyponatremia) AND (sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic *[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp])])

#17 Search (hypokalemia) AND (sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic *[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp])

#18 Search (hyperkalemia) AND (sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic *[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp])

#19 Search (hyperkalemia) AND (sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic *[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp])

#20 Search #16 OR #17 OR #18 OR #19

#2 Search "Sensitivity and Specificity"[MESH]

#22 Search "Observer Variation"[MESH]

Appendix 4.1a (continued) PubMed search strategy for determinants of seasonal fluctuations in sodium and potassium levels in children less than 2 years old with diarrhoea: period 1966 to April 2005

#23 Search #15 OR #21 OR #22

#24 Search "Diarrhea, Infantile"[MESH] Field: All Fields, Limits: Humans

#26 Search #20 AND #24

#27 Search #13 AND #24

#31 Search #21 OR #22

#32 Search #31 OR #13

#33 Search #24 AND #32 Field: All Fields, Limits: Humans

#34 Search #26 OR #33 Limits: Humans

Appendix 4.1b PubMed search strategy for determinants of seasonal fluctuations in sodium and potassium levels in children less than 2years old: period 1966 to December 2005

#1 Search (hypokalaemia) AND (sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic *[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp]) Field: All Fields, Limits: All Infant: birth-23 months, Humans

#2 Search (hypernatraemia) AND (sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic *[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp]) Limits: All Infant: birth-23 months, Humans

#3 Search (hyponatraemia) AND (sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic *[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp]) Limits: All Infant: birth-23 months, Humans

Appendix 4.2 Contingency tables for data extracted from Hill *et al.* (1981) and Tjon A Ten (1999) to calculate measures of diagnostic accuracy

Hill *et al.* (1981)

Sign (n)	Hypernatraemic (sodium >150 mmol/l)	Not hypernatraemic
*Jittery (n= 154)		
Jittery	15	0
Normal	91	48
Total	**106**	**48**
†Coma/convulsion/drowsy (n=182)		
Coma/convulsion/drowsy	41	2
Normal	91	48
Total	**132**	**50**

*All patients with coma/convulsion/drowsy removed (n=41) and data for 2 patients was missing.
†All jittery patients removed (n=15).

Tjon A Ten (1999)

Signs (n)	Hypernatraemia (sodium >150 mmol/l)	No hypernatraemia
*Dehydration (n=265)		
Present	5	3
Absent	69	188
Total	**74**	**191**

* Assuming that 73 patients with data missing for sodium concentrations were normal.

Appendix 4.3 Information provided to medical officers at the beginning of their ward rotation (2 months) in the Rehydration Unit

Gastro Electrolyte Study - Ward A9

Why do the study?

The ***main clinical objective*** is to assess the usefulness of clinical signs of hypokalaemia and hypernatraemia. The 'classical' clinical signs have not actually been tested to see how accurate they are (if at all). This knowledge would help clinicians manage patients better and enable better guidelines for electrolyte testing.

What are admitting doctors asked to do?

1. Complete the ***tick chart*** (including time and doctor's name) inserted into the A9 clerking notes.
2. We may also ask you to complete a tick chart on a small sample of patients admitted by someone else (to see how much variation there is in eliciting different signs). If you will be unable to do so within 30 minutes of the admission examination, please let us know.
3. Take ***blood for gases and electrolytes*** in the minority of children in whom it would not usually be done. (The researchers will obtain informed consent.)

Why should the admitting doctors do this?

- For the study findings to be generalisable to actual practice, the clinical signs need to be elicited by a *range* of clinicians who would normally see the children in actual practice.
- We are asking admitting doctors to take the blood as a favour (Victoria Pillay is not a doctor or nurse). If you are unwilling to do this in children who would not usually have blood taken (approx. 10-20% of admissions), please let us know and we will make an alternative arrangement.

The investigators

Victoria Pillay is enrolling patients and collecting data. Her co-investigator is George Swingler.

Please do not hesitate to contact Victoria Pillay (ext 5120) or George Swingler (ext 5306) if you have any questions or reservations about the study.

Explanatory notes

- The ***tick chart*** records the doctors' findings of the clinical signs that we are testing, and takes two to three minutes to complete. We plan to enrol children between 11:00 and 19:00 on each working day.
- ***It is important that you DO NOT KNOW the sodium and potassium levels when eliciting the signs***, otherwise this knowledge will unconsciously influence your findings. For this reason, a "Post It" slip will be placed over results in the notes. *If you happen to know the electrolyte results, please tell Victoria and she'll make another plan.*
- ***The clinical signs are being tested, not the doctors.*** The doctor's name is needed to describe (anonymously) how many doctors took part and how many patients each saw. *We shall not analyse individual doctors' performance.*

Appendix 4.4 Gastro Electrolyte Study: CLINICAL DETAILS

Date: / / _____ **Time:** _____

Name _____

Folder No _____

D.O.B _____ R/S ___

Examining doctor: _____

Level of consciousness		Tick
Eyes opening	Spontaneously	4
	To speech	3
	To pain	2
	No response	1
Best motor response	Obeys/normal spontaneous movement	6
	Localises pain	5
	Flexion withdrawal	4
	Flexor posturing	3
	Extensor posturing	2
	No response	1
Best verbal response	Coos and babbles	5
	Irritable/cries	4
	Cries to pain	3
	Grunts	2
	No response	1

Reflexes: Test one biceps and one knee, check other side only if unsure.

	Reduced	Normal	Brisk
Biceps	0	1	2
Knee	0	1	2

	Yes	*±*	*No*	*N/A*	*Not Elicited*
Weakness					
Resists procedures (e.g. taking blood)	0	1	2	9	3
Kicks away (complete leg extension from flexion)	0	1	2	9	3
Pushes away (gravity overcome)	0	1	2	9	3
Lifts head from bed (prone, ≥ 6 weeks)	0	1	2	9	3
Sits unsupported (≥ 7 months)	0	1	2	9	3
Rolls over (≥ 9 months)	0	1	2	9	3
Stands (≥ 12 months)	0	1	2	9	3
Tone					
Lies in frog's legs position	2	1	0	9	3
Marked head lag on pulling to sit (if >3 months)	2	1	0	9	3
Marked truncal slump on sitting (if > 7 months)	2	1	0	9	3
Wooden feel to skin	2	1	0	9	3
Ileus	2	1	0		3
Abdominal distension (in non-obese child, elevation of the abdominal wall above the level of the xiphisternum when viewed from the side)	2	1	0		3

Appendix 4.5 Contingency tables used to calculate weighted Kappa scores for the each clinical assessment performed by medical officers independently and blind

Dr A ↓ / Dr B →	Level of consciousness scale			
	15	14	13	**Total**
15	11	8	0	19
14	3	25	1	29
13	1	1	0	2
Total	15	34	1	**50**

Dr A ↓ / Dr B →	Lies in a frog's legs position				
	Yes	Maybe	No	Not done	**Total**
Yes	39	2	2	0	43
Maybe	5	0	0	0	5
No	1	0	1	0	2
Not Done	0	0	0	0	0
Total	45	2	3	0	**50**

Dr A ↓ / Dr B →	Marked headlag				
	Yes	Maybe	No	Not done	**Total**
Yes	2	1	5	0	8
Maybe	1	3	2	0	6
No	1	5	26	0	32
Not Done	0	0	0	4	4
Total	4	9	33	4	**50**

Dr A ↓ / Dr B →	Truncal Slump				
	Yes	Maybe	No	Not done	**Total**
Yes	31	0	0	0	31
Maybe	4	0	0	0	4
No	2	0	1	0	3
Not Done	0	0	0	12	12
Total	37	0	1	12	**50**

Appendix 4.5 (continued) Contingency tables used to calculate weighted Kappa scores for the each clinical assessment performed by medical officers independently and blind

Resists procedure

Dr A ↓ / Dr B →	Yes	Maybe	No	Not done	**Total**
Yes	8	3	1	17	29
Maybe	2	0	0	4	6
No	0	0	0	0	0
Not Done	12	2	1	0	15
Total	22	5	2	21	**50**

Kicks away

Dr A ↓ / Dr B →	Yes	Maybe	No	Not done	**Total**
Yes	35	3	0	0	38
Maybe	3	1	2	0	6
No	3	0	1	0	4
Not Done	2	0	0	0	2
Total	43	4	3	0	**50**

Pushes Away

Dr A ↓ / Dr B →	Yes	Maybe	No	Not done	**Total**
Yes	32	3	5	0	40
Maybe	3	2	1	0	6
No	3	1	0	0	4
Not Done	0	0	0	0	0
Total	38	6	6	0	**50**

Lifts head from bed

Dr A ↓ / Dr B →	Yes	Maybe	No	Not done	**Total**
Yes	33	0	3	0	36
Maybe	4	0	1	0	5
No	3	2	3	0	8
Not Done	0	0	1	0	1
Total	40	2	8	0	**50**

Appendix 4.5 (continued) Contingency tables used to calculate weighted Kappa scores for the each clinical assessment performed by medical officers independently and blind

Sits unsupported

Dr A ↓ / Dr B →	Yes	Maybe	No	Not done	**Total**
Yes	35	0	0	0	35
Maybe	0	0	0	0	0
No	2	0	1	0	3
Not Done	0	0	0	12	12
Total	37	0	1	12	**50**

Rolls over

Dr A ↓ / Dr B →	Yes	Maybe	No	Not done	**Total**
Yes	11	6	2	0	19
Maybe	1	1	1	1	4
No	6	1	0	0	7
Not Done	0	1	0	19	20
Total	18	9	3	20	**50**

Stands

Dr A ↓ / Dr B →	Yes	Maybe	No	Not done	**Total**
Yes	13	0	1	0	14
Maybe	4	3	2	0	9
No	2	1	3	0	6
Not Done	0	1	0	20	21
Total	19	5	6	20	**50**

Ileus

Dr A ↓ / Dr B →	Yes	Maybe	No	Not done	**Total**
Yes	37	3	0	0	40
Maybe	4	2	0	0	6
No	3	1	0	0	4
Not Done	0	0	0	0	0
Total	44	6	0	0	**50**

Appendix 4.5 (continued) Contingency tables used to calculate weighted Kappa scores for the each clinical assessment performed by medical officers independently and blind

Abdominal distension

Dr A ↓ / Dr B →	Yes	Maybe	No	Not done	**Total**
Yes	22	3	3	0	28
Maybe	4	7	4	0	15
No	1	2	4	0	7
Not Done	0	0	0	0	0
Total	27	12	11	0	**50**

Wooden feel to the skin

Dr A ↓ / Dr B →	Yes	Maybe	No	Not done	**Total**
Yes	42	1	1	0	44
Maybe	4	0	0	0	4
No	2	0	0	0	2
Not Done	0	0	0	0	0
Total	48	1	1	0	**50**

Biceps, tendon reflexes

Dr A ↓ / Dr B →	Reduced	Normal	Brisk	Not done	**Total**
Reduced	2	10	1	0	13
Normal	4	28	3	1	36
Brisk	1	0	0	0	1
Not done	0	0	0	0	0
Total	7	38	4	1	**50**

Knee, tendon reflexes

Dr A ↓ / Dr B →	Reduced	Normal	Brisk	Not done	**Total**
Reduced	4	7	1	0	12
Normal	5	23	4	1	33
Brisk	0	4	1	0	5
Not done	0	0	0	0	0
Total	9	34	6	1	**50**

Appendix 4.6 Tables for the assessment (performed by medical officers) for each clinical sign that was used to calculate likelihood ratios for hyponatraemia

Sign	Levels	Hyponatraemic	Not hyponatraemic	N
Irritable	Yes	76	174	
	None	50	52	
	Not reported	61	62	
		187	**288**	**475**
Seizures	Yes	8	20	
	No	177	266	
	Not reported	2	2	
		187	**288**	**475**
Level of consciousness (Glasgow Coma Score)	<8	3	1	
	8 ≤12	9	28	
	>12	175	256	
	Not reported	0	3	
		187	**288**	**475**
Resists procedure	Present	141	207	
	Uncertain	21	37	
	Absent	12	12	
	Not reported	13	32	
		187	**288**	**475**
Kicks away	Present	134	205	
	Uncertain	23	39	
	Absent	29	40	
	Not reported	1	4	
		187	**288**	**475**
Pushes away	Present	138	195	
	Uncertain	27	50	
	Absent	21	39	
	Not reported	1	4	
		187	**288**	**475**

Appendix 4.6 (continued) Tables for the assessment (performed by medical officers) for each clinical sign that was used to calculate likelihood ratios for hyponatraemia

Sign	Levels	Hyponatraemic	Not hyponatraemic	N
Lifts head from bed	Present	128	173	
	Uncertain	16	33	
	Absent	41	78	
	Not reported	2	4	
		187	**288**	**475**
Sits unsupported	Present	127	125	
	Uncertain	3	10	
	Absent	14	19	
	Not reported	2	2	
		146	**156**	**302**
Rolls over	Present	85	82	
	Uncertain	16	13	
	Absent	22	14	
	Not reported	10	10	
		133	**119**	**252**
Stands	Present	58	57	
	Uncertain	13	7	
	Absent	28	17	
	Not reported	3	1	
		102	**82**	**184**
Wooden feel to the skin	Absent	161	260	
	Uncertain	10	15	
	Present	16	10	
	Not reported	0	3	
		187	**288**	**475**

Appendix 4.6 (continued) Tables for the assessment (performed by medical officers) for each clinical sign that was used to calculate likelihood ratios for hyponatraemia

Sign	Levels	Hyponatraemic	Not hyponatraemic	N
Biceps, tendon reflexes	Reduced	35	57	
	Normal	133	191	
	Brisk	12	28	
	Not reported	7	12	
		187	**288**	**475**
Knee, tendon reflexes	Reduced	33	45	
	Normal	128	173	
	Brisk	22	57	
	Not reported	4	13	
		187	**288**	**475**
Degree of dehydration	>10%	34	45	
	5%	98	151	
	Potentially	45	98	
	Good	16	35	
	Not reported	3	3	
		196	**332**	**528**
Peripheral perfusion	Poor	19	27	
	Fair	92	97	
	Good	80	200	
	Not reported	0	13	
		191	**337**	**528**

Appendix 4.7 Tables for the assessment (performed by medical officers) for each clinical sign that was used to calculate likelihood ratios for hypernatraemia

Sign	Levels	Hypernatraemic	Not hypernatraemic	N
Irritable	Yes	19	231	
	None	4	98	
	Not reported	8	115	
		31	**444**	**475**
Seizures	Yes	2	26	
	No	29	414	
	Not reported	0	4	
		31	**444**	**475**
Level of consciousness	<8	0	4	
(Glasgow Coma Score)	8 ≤12	5	32	
	>12	26	405	
	Not reported	0	3	
		31	**444**	**475**
Resists procedure	Present	21	327	
	Uncertain	5	53	
	Absent	2	22	
	Not reported	3	42	
		31	**444**	**475**
Kicks away	Present	18	321	
	Uncertain	6	56	
	Absent	7	62	
	Not reported	0	5	
		31	**444**	**475**
Pushes away	Present	15	318	
	Uncertain	6	71	
	Absent	9	51	
	Not reported	1	4	
		31	**444**	**475**
Lifts head from bed	Present	10	291	
	Uncertain	5	44	
	Absent	16	103	
	Not reported	0	6	
		31	**444**	**475**

Appendix 4.7 (continued) Tables for the assessment (performed by medical officers) for each clinical that was used to calculate likelihood ratios for hypernatremia

Sign	Levels	Hypernatraemic	Not hypernatraemic	N
Sits unsupported	Present	4	248	
	Uncertain	0	13	
	Absent	3	30	
	Not reported	0	4	
		7	**295**	**302**
Rolls over	Present	2	165	
	Uncertain	1	28	
	Absent	1	35	
	Not reported	1	19	
		5	**247**	**252**
Stands	Present	2	113	
	Uncertain	0	20	
	Absent	2	43	
	Not reported	0	4	
		4	**180**	**184**
Wooden feel to the skin	Absent	25	396	
	Uncertain	3	22	
	Present	3	23	
	Not reported	0	3	
		31	**444**	**475**
Biceps, tendon reflexes	Reduced	7	85	
	Normal	17	307	
	Brisk	5	35	
	Not reported	2	17	
		31	**444**	**475**
Knee, tendon reflexes	Reduced	3	75	
	Normal	16	285	
	Brisk	9	70	
	Not reported	3	14	
		31	**444**	**475**

Appendix 4.7 (continued) Tables for the assessment (performed by medical officers) for each clinical that was used to calculate likelihood ratios for hypernatremia

Sign	Levels	Hypernatraemic	Not hypernatraemic	N
Degree of dehydration	≥10%	10	69	
	5%	22	227	
	Potentially	4	139	
	Good	1	50	
	Not reported	0	6	
		37	**491**	**528**
Peripheral perfusion	Poor	7	39	
	Fair	11	178	
	Good	19	261	
	Not reported	0	13	
		37	**491**	**528**

Appendix 4.8 Tables for the assessment (performed by medical officers) for each clinical sign that was used to calculate likelihood ratios for severe hypernatraemia

Sign	Levels	Severely hypernatraemic	Not severely hypernatraemic	N
Irritable	Yes	12	238	
	None	1	101	
	Not reported	2	121	
		15	**460**	**475**
Seizures	Yes	0	28	
	No	15	428	
	Not reported	0	4	
		15	**460**	**475**
Level of consciousness (Glasgow Coma Score)	<8	0	4	
	8 ≤12	2	35	
	>12	13	418	
	Not reported	0	3	
		15	**460**	**475**
Resists procedure	Present	9	339	
	Uncertain	3	55	
	Absent	1	23	
	Not reported	2	43	
		15	**460**	**475**
Kicks away	Present	10	329	
	Uncertain	2	60	
	Absent	3	66	
	Not reported	0	5	
		15	**460**	**475**
Pushes away	Present	8	325	
	Uncertain	4	73	
	Absent	3	57	
	Not reported	0	5	
		15	**460**	**475**
Lifts head from bed	Present	4	297	
	Uncertain	4	45	
	Absent	7	112	
	Not reported	0	6	
		15	**460**	**475**

Appendix 4.8 (continued) Tables for the assessment (performed by medical officers) for each clinical sign that was used to calculate likelihood ratios for severe hypernatraemia

Sign	Levels	Severely hypernatraemic	Not severely hypernatraemic	N
Sits unsupported	Present	1	251	
	Uncertain	0	13	
	Absent	0	33	
	Not reported	0	4	
		1	**301**	**302**
Rolls over	Present	1	166	
	Uncertain	0	29	
	Absent	0	36	
	Not reported	0	20	
		1	**251**	**252**
Stands	Present	1	114	
	Uncertain	0	20	
	Absent	0	45	
	Not reported	1	3	
		2	**182**	**184**
Wooden feel to the skin	Absent	11	410	
	Uncertain	3	22	
	Present	1	25	
	Not reported	0	3	
		15	**460**	**475**
Biceps, tendon reflexes	Reduced	4	88	
	Normal	7	317	
	Brisk	3	37	
	Not reported	1	18	
		15	**460**	**475**
Knee, tendon reflexes	Reduced	2	76	
	Normal	8	293	
	Brisk	4	75	
	Not reported	1	16	
		15	**460**	**475**

Appendix 4.8 (continued) Tables for the assessment (performed by medical officers) for each clinical sign that was used to calculate likelihood ratios for severe hypernatraemia

Sign	Levels	Severely hypernatraemic	Not severely hypernatraemic	N
Degree of dehydration	≥10%	5	74	
	5%	12	237	
	Potentially	0	143	
	Good	0	51	
	Not reported	0	6	
		17	**511**	**528**
Peripheral perfusion	Poor	5	41	
	Fair	4	185	
	Good	8	272	
	Not reported	0	13	
		17	**511**	**528**

Appendix 4.9 Tables for the assessment (performed by medical officers) for each clinical sign that was used to calculate likelihood ratios for hypokalaemia

Sign	Levels	Hypokalaemic	Not hypokalaemic	N
Level of consciousness (Glasgow Coma Score)	<8	0	4	
	8 ≤12	18	19	
	>12	210	217	
	Not reported	3	0	
		231	**240**	**471**
Lies in frog's legs position	Absent	166	179	
	Uncertain	34	26	
	Present	33	27	
	Not reported	3	3	
		236	**235**	**471**
Marked headlag	Absent	115	127	
	Uncertain	40	26	
	Present	65	46	
	Not reported	3	4	
		223	**203**	**426**
Truncal slump	Absent	108	92	
	Uncertain	29	15	
	Present	28	17	
	Not reported	5	5	
		170	**129**	**299**
Resists procedure	Present	166	179	
	Uncertain	35	23	
	Absent	15	9	
	Not reported	20	24	
		236	**235**	**471**
Kicks away	Present	163	172	
	Uncertain	32	30	
	Absent	41	28	
	Not reported	0	5	
		236	**235**	**471**

Appendix 4.9 (continued) Tables for the assessment (performed by medical officers) for each clinical sign that was used to calculate likelihood ratios for hypokalaemia

Sign	Levels	Hypokalaemic	Not hypokalaemic	N
Pushes away	Present	160	171	
	Uncertain	44	32	
	Absent	30	29	
	Not reported	2	3	
		236	**235**	**471**
Lifts head from bed	Present	150	148	
	Uncertain	25	24	
	Absent	59	59	
	Not reported	2	4	
		236	**235**	**471**
Sits unsupported	Present	143	107	
	Uncertain	8	5	
	Absent	18	14	
	Not reported	1	3	
		170	**129**	**299**
Rolls over	Present	94	71	
	Uncertain	19	10	
	Absent	20	17	
	Not reported	13	7	
		146	**105**	**251**
Stands	Present	62	52	
	Uncertain	17	3	
	Absent	33	13	
	Not reported	3	1	
		115	**69**	**184**
Ileus	Absent	211	221	
	Uncertain	16	11	
	Present	6	2	
	Not reported	3	1	
		236	**235**	**471**

Appendix 4.9 (continued) Tables for the assessment (performed by medical officers) for each clinical sign that was used to calculate likelihood ratios for hypokalaemia

Sign	Levels	Hypokalaemic	Not hypokalaemic	N
Abdominal distension	Absent	178	202	
	Uncertain	29	14	
	Present	28	19	
	Not reported	1	0	
		236	**235**	**471**
Degree of dehydration	≥10%	49	31	
	5%	133	113	
	Potentially	54	88	
	Good	18	33	
	Not reported	2	4	
		256	**269**	**525**
Peripheral perfusion	Poor	25	21	
	Fair	109	80	
	Good	117	160	
	Not reported	5	8	
		256	**269**	**525**

Appendix 4.10 Tables for the assessment (performed by medical officers) for each clinical sign that was used to calculate likelihood ratios for severe hypokalaemia

Sign	Levels	Severely hypokalaemic	Not severely hypokalaemic	N
Level of consciousness (Glasgow Coma Score)	<8	4	0	
	8 ≤12	9	28	
	>12	74	353	
	Not reported	2	1	
		89	**382**	**471**
Lies in frog's legs position	Absent	56	289	
	Uncertain	16	44	
	Present	16	44	
	Not reported	1	5	
		89	**382**	**471**
Marked headlag	Absent	34	208	
	Uncertain	14	52	
	Present	37	74	
	Not reported	1	6	
		86	**340**	**426**
Truncal slump	Absent	36	164	
	Uncertain	13	31	
	Present	21	24	
	Not reported	1	9	
		71	**228**	**299**
Resists procedure	Present	49	296	
	Uncertain	20	38	
	Absent	9	15	
	Not reported	11	33	
		89	**382**	**471**
Kicks away	Present	49	286	
	Uncertain	20	42	
	Absent	20	49	
	Not reported	0	5	
		89	**382**	**471**

Appendix 4.10 (continued) Tables for the assessment (performed by medical officers) for each clinical sign that was used to calculate likelihood ratios for severe hypokalaemia

Sign	Levels	Severely hypokalaemic	Not severely hypokalaemic	N
Pushes away	Present	46	285	
	Uncertain	26	50	
	Absent	17	42	
	Not reported	0	5	
		89	**382**	**471**
Lifts head from bed	Present	44	254	
	Uncertain	12	37	
	Absent	32	86	
	Not reported	1	5	
		89	**382**	**471**
Sits unsupported	Present	55	195	
	Uncertain	3	10	
	Absent	13	19	
	Not reported	3	1	
		74	**225**	**299**
Rolls over	Present	35	130	
	Uncertain	8	21	
	Absent	10	27	
	Not reported	8	12	
		61	**190**	**251**
Stands	Present	21	93	
	Uncertain	8	12	
	Absent	15	31	
	Not reported	2	2	
		46	**138**	**184**
Ileus	Absent	77	355	
	Uncertain	9	18	
	Present	2	6	
	Not reported	1	3	
		89	**382**	**471**

Appendix 4.10 (continued) Tables for the assessment (performed by medical officers) for each clinical sign that was used to calculate likelihood ratios for severe hypokalaemia

Sign	Levels	Severely hypokalaemic	Not severely hypokalaemic	N
Abdominal distension	Absent	64	316	
	Uncertain	13	30	
	Present	11	36	
	Not reported	1	0	
		89	**382**	**471**
Degree of dehydration	≥10%	25	55	
	5%	48	198	
	Potentially	14	128	
	Good	4	47	
	Not reported	2	4	
		93	**432**	**525**
Peripheral perfusion	Poor	16	30	
	Fair	48	141	
	Good	26	251	
	Not reported	3	10	
		93	**432**	**525**

APPENDICES: CHAPTER FIVE

Appendix 5.1 PubMed search strategy on the therapeutic impact of routine electrolyte testing: period 1966 to June 2005

#7 Search Diarrhoea

#9 Search "Diarrhea, Infantile"[MeSH]

#10 Search ("Sodium/blood"[MeSH] OR "Sodium/therapeutic use"[MeSH])

#11 Search ("Potassium/blood"[MeSH] OR "Sodium/therapeutic use"[MeSH])

#12 Search "Hypernatremia"[MeSH]

#13 Search "Hyponatremia"[MeSH]

#14 Search "Hypokalemia"[MeSH]

#23 Search "therapeutic use"[Subheading]

#24 Search #7 AND #9

#25 Search #10 OR #11

#26 Search #7 OR #9

#27 Search #12 OR #13 OR #14

#28 Search #25 AND #26

#29 Search #26AND #27

#30 Search #26 AND #27

#33 Search "Electrolytes/diagnostic use"[MeSH]

#34 Search "Electrolytes/therapeutic use"[MeSH]

#35 Search #33 AND #34

#36 Search #26 AND #35

#37 Search #27 AND #23

#38 Search #34 AND #26

#39 Search "Potassium/blood"[MESH]

#40 Search "Sodium/blood"[MESH]

#41 Search #39 OR #40

#42 Search #41 AND #26

#43 Search #42 AND #34

#44 Search #26 AND #34

#45 Search #30 AND #34

#48 Search #28 OR #45 OR #43 Limits: Humans

Appendix 5.2 Extracted from the Rehydration Unit protocol for the management of sodium and potassium disturbances in children with diarrhoea

Hypokalaemia

If potassium < 3.0 mmol/l

OR

potassium <4.0 mmol/l AND base deficit >10

i. KCl 100 mg/kg/dose 6hrly orally x 2 days (max 750 mg or 3 g daily)

If potassium < 2.0 mmol/l

i. oral KCl as above

ii. IV KCl: 2 ml KCl (15% solution) added to 200 ml 1/2 DD. NEVER EXCEED THIS DOSE UNLESS DISCUSSED WITH REGISTRAR.

iii. check potassium 4-hourly

If potassium <1.5 mmol/l

i. As above

ii. ECG monitor and inform registrar

Hyponatraemia

If sodium < 125 mmol/l

i. *If IVI fluids*: Normal saline 200 ml bag + 2 ml 15% KCl and 20 ml of 50% dextrose water, at usual rate for rehydration.
If NG fluids: Continue with 1/2 DD and recheck sodium in 4-6 hours. If sodium has fallen further change to IV fluids.

ii. Change back to 1/2 DD once the sodium is > 130 mmol/l.

Hypernatraemia

If sodium > 150 mmol/l

i. Use 1/2 DD (NOT 5% dextrose water) for rehydration. Treat shock with volume expanders as usual.

ii. Calculate fluid administration rates as usual according to clinical assessment of dehydration (remember that it is easy to underestimate dehydration in hypernatraemia).

iii. Check serum sodium 4-hourly if Na >155 mmol/l. The sodium should drop by 1-2 mmol/h. Too rapid a fall leads to cerebral oedema and convulsions, while failure of the sodium to drop means that the patient needs more fluid.

iv. Ensure hypovolaemia is corrected. Urine output should be $\geq$2 ml/kg/h.

v. Use soda bicarbonate only if pH <7.10. Half correct the acidosis.

Appendix 5.3 Booklet used to record clinical notes of patients admitted to the Rehydration Unit at Red Cross Children's Hospital

NAME: FOLDER NO: D.O.B.: (USE STICKER IF AVAILABLE)	MEASLES: DISEASE: NO / YES VACCINE: NO / YES - 7/12 14/12 TB CONTRACT: NO / YES IMMUNISATIONS: COMPLETE / INCOMPLETE

RECORD OF DIARRHOEAL DISEASE

NO	ADMISSION		DISCHARGE / TRANSFER			COMPLICATIONS RELATED TO DIARRHOEA
	DATE	WT	DATE	WT	FEED	eg. Shock, hypernatraemia, Ac. Renal Failure
1						
2						
3						
4						
5						
6						

PROBLEMS OTHER THAN DIARRHOEAL DISEASE

DATE	PROBLEM	IF UNRESOLVED ON DISCHARGE: PLAN

ACID -BASE AND ELECTROLYTE RESULTS

DATE	TIME	pH	PCO2	BE	SB	Na^+	K^+	SODA BIC GIVEN

OTHER INVESTIGATIONS

DATE	INVEST.	RESULT	DATE	INVEST.	RESULT

FIRST ADMISSION /RE-ADMISSION: DATE:_____

P.C. 1. DIARRHOEA_____DAYS_____COLOUR_____CONSISTENCY

BLOOD: YES/NO MUCUS: YES/NO WORMS: YES/NO

2. VOMITING: _____DAYS BILE: YES/NO

3. FOODS:_____

4. OTHER PROBLEMS:_____

_____

_____

EXAMINATION

1.	HYDRATION	GOOD	POT DEHYD	5%	10%	>10%
2.	NUTRITION	NORMAL	UNDER WT FOR AGE	MARASMIC	KWASH	MARASMIC KWASH

3. CVS

PERIPHERAL PERFUSION:

GOOD	POOR	FAIR

Pulse _____/ MIN BP:_____

4. RESP SYSTEM: RESP RATE: _____/ MIN

5. ABDOMEN:

6. ENT:

7. CNS:

8. OTHER:

N.B. NOW COMPLETE PROBLEM LIST ON FIRST PAGE

ASSESSMENT SHOCKED: YES/NO DEHYDRATION: %

OTHER PROBLEMS: _____

_____

_____

_____

INITIAL FLUID THERAPY PLAN:

PLASMA VOLUME EXPANDER FOR SHOCK	ORAL 1/2DD AND REASSESS	NPM AND IVI FLUIDS ONLY	NG AND ORAL FLUIDS	Na BIC. _____ml

FLUID SCHEDULE

DATE	BOTTLE NO	FLUID	ADDITIVES	VOLUME	HOURS TO RUN IN	RATE DROPS / MIN	TIME STARTED	TIME COMPLETED	SIG.

DRIP ROOM CONTINUING ASSESSMENT **DRX 274**

DATE/DAY: _____

TIME	AM/PM	AM/PM	AM/PM
WEIGHT			
TEMPERATURE			
VOMITING			
STOOLS			
PERIPHERAL CIRC			
DEHYDRATION			
REHYD VOL			
MAINT VOL			
TOTAL / 24 HRS			
ORAL FEEDS			
MANAGEMENT a) CURRENT PROBLEM b) ASSESSMENT OF PATIENT c) PLAN / TREATMENT			
SIGNATURE:			

Appendix 5.4 Gastro Electrolyte Study: FOLDER INFORMATION

ON ☐

Name:_____

Folder No:_____

D.O.B:_____ R/S:___

Date(s) folder examined:_____/ /_____

Date(s) data entered onto database: ____/ /_____

Na+ on admission:_____ **normal 135 – 150**

K+ on admission:_____ **normal 3.5 – 5.3**

Date blood taken:_____/ /_____ Time:_____

Date baby examined:____/ /_____ Time: _____

Time difference: _____

Potassium less than 3.5 mmol/l on admission? **Y / N**

If 'Yes'

highest daily dose of oral KCl_____

daily dose above 1.5 g **Y / N**

IV fluid containing more than 17 mmol/l of potassium **Y / N**

(½ DD = 17 K^+)

Potassium less than 2.5 mmol/l on admission **Y / N**

If 'Yes'

Admission to ICU **Y / N**

If 'Yes'

Mention of the K+ level in the clinical notes **before** or **at the time of** the ICU admission decision? **Y / N**

Sodium less than 135 mmol/l on admission **Y / N**

If 'Yes'

IV fluid containing more than 61 mmol/l of sodium **Y / N**

(½ DD = 61 Na^+)

Sodium more than 150 mmol/l on admission **Y / N**

If 'Yes'

at least one repeat sodium measurement **Y / N**

Sodium more than 158 mmol/l on admission Y / N

If 'Yes'

Admission to ICU Y / N

If 'Yes'

Mention of the Na+ level in the clinical notes **before** or **at the time of** the ICU admission decision. **Y / N**

Outcome

Discharge from A9	Date: ___/ /_____
Died in A9	Date: ___/ /_____
Transfer out to Ward/Hosp	Date: ___/ /_____
	Where:_____
ICU	Date:___/ /_____

Weight on admission: _____

Weight on discharge: _____

Length:_____

Presence of co-morbidity:_____

_____

_____

Presence of shock: **Y / N**

Hydration	Good	Pot. Dehyd	5%	10%	>10%
Nutrition	Normal	UWFA	Marasmic	Kwash	Maras/Kwash

Peripheral perfusion: Good / fair / poor.

HIV status: (Baby) - Positive = 1

Test: _____

Negative =2

Test: _____

Unknown = 3

HIV status: (Mom) - Positive = 1

Test: _____

Negative =2

Test: _____

Unknown = 3

Tests for HIV: PCR=1; P4=2; Elisa=3; Rapid test=4; Not reported=5; Other=6.

Medical emergency : **Y / N**

Time: _____

Time Difference: _____