Diarrhoeal Diseases in Low- and Middle-income Countries

Trends, Management and Control

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Trends, Management and Control

Stockholm 2007
The picture on the cover page is from a flip chart developed in 1985 in Pakistan with support from UNICEF.
Four years old
Sitting in the sofa next to my mother Sigrid
She is quietly reading to me - Peter Plys - Winnie the Pooh
Through the window - the big elm trees, the fields, horizon, the sky.
Serenity - Protection.

To Mothers,
mine in particular
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ABSTRACT

Background: Diarrhoeal diseases constitute a major disease burden on children in low- and middle-income countries (LMC), with an estimated 2 million 0-4 years old dying annually due to diarrhoea. Dehydration is the main cause of these deaths. An oral remedy based on glucose and sodium to treat dehydration was developed in the 1960s. Significant efforts have since been made to promote the use of Oral Rehydration Therapy (ORT). Adoption of ORT has lead to significant child mortality reductions. Meanwhile, little change in diarrhoea morbidity in LMC has been reported.

Main aim: The main aim of this thesis is to make a contribution to improved child health in low- and middle-income countries by enhancing knowledge on diarrhoeal diseases control, especially on case management and morbidity reductions.

Methods: The first two studies were conducted in Northeastern (NE) Brazil, a region of 9 states and a population of 51 million. The first study evaluated diarrhoea case management through a household cluster survey of 6,524 children 0-4 years old. The second study used a health facility survey to assess quality of diarrhoea child care in 78 randomly selected primary care facilities. The third study was methodological and analysed paired results from two types of household surveys in eight countries to assess their validity. In the fourth study, diarrhoea management in LMC from 1986 to 2003 was analysed for four variables from up to 107 cross-sectional surveys. In the fifth study three indicators of diarrhoea morbidity in the state of Ceará in NE Brazil were assessed for trends 1998-2005 and the association between determinants and morbidity studied.

Results: The household survey in NE Brazil showed that 982 children (15%) had suffered from diarrhoea during 15 days preceding the interview. ORT was given to 24%. 95% of the caretakers knew about rehydration solutions, but only 18% prepared them correctly, the most common error being the use of insufficient water. The health facility survey in NE Brazil showed that case management based on ORT was established in health services but also pointed to deficiencies in management. Utensils for administration of ORT were available in only half of the facilities. Health workers showed deficiencies in history taking, examination and communication to parents. Still, in 84% of 75 observed child visits ORT was prescribed. In the study on results from comparable surveys, around half of the survey pairs showed a statistically significant variation, rejecting a hypothesis of no difference. This pointed to the possibility of systematic errors in data collection in household surveys. The study of data on case management from household surveys showed limited progress in diarrhoea management in LMC 1986–2003. Achievements in ORT use were far below global targets set at the beginning of the 1990s. An estimated 307 million children did not get ORT and 356 million did not get more to drink during diarrhoea at the beginning of the 21st century. The study in Ceará, Brazil provided some evidence that diarrhoea morbidity went down slightly 1998-2005. The decline was strongest for diarrhoea admissions. Few determinants of morbidity could be associated with the three indicators of diarrhoea morbidity.

Conclusions: This thesis has pointed to achievements and problems in diarrhoeal diseases control from 1986 to 2005. ORT became well known in that period. At the same time, unsatisfactory adoption and application of ORT in the late 1980s documented from Brazil persisted in most LMC over the 1990s. Also, diarrhoea case management was found to meet logistical and managerial problems in primary health services, contributing to inadequate utilization of ORT. Much more research is needed on how to improve diarrhoea case management LMC.

Findings from Ceará, Brazil in the thesis support other studies that have shown limited decline in diarrhoea morbidity in LMC. More research is needed on the interaction between morbidity, case management and mortality for proper understanding of priority setting in diarrhoea control. Efforts to reduce diarrhoea morbidity should be further strengthened, especially among the poorest.

The thesis has also documented the need for further research on how to strengthen the methodology of household surveys, a key instrument in impact evaluation.

The thesis highlights that there is little time for complacency in strengthening diarrhoeal diseases control. Around 300 million children in the LMC appear not to get Oral Rehydration Therapy, the treatment that is essential for prevention of death from diarrhoea. This fact should lead international organisations, donors and national governments to again give high priority to diarrhoeal diseases, especially in low-income countries where diarrhoea is a daily life-threatening condition to many children.

Keywords: Diarrhoea, Case management, ORT, Diarrhoea morbidity, Brazil, Low- and middle-income countries, Community, Households, Primary care
LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to by their Roman numerals I-V.


All previously published papers have been reprinted with permission from the respective publisher.
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>AIDS</td>
<td>Aquired Immune Deficiency Syndrome</td>
<td>A viral disease that attacks the immune system and when untreated leads to serious impairments and ultimately death after some years of infection.</td>
</tr>
<tr>
<td>ARI</td>
<td>Acute Respiratory Infections</td>
<td>Infections affecting the respiratory organs and creating short-term illness of varying degree of severity.</td>
</tr>
<tr>
<td>BPL</td>
<td>Below Poverty Line</td>
<td>People with an income falling below an income defined as poverty by a government institution</td>
</tr>
<tr>
<td>CDD</td>
<td>Programme for Control of Diarrhoeal Diseases</td>
<td>A programme initiated in 1980 by WHO for control of diarrhoeal diseases and later adopted by many low- and middle-income countries.</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
<td>A statistical measurement of an interval of values of a variable, usually around the mean.</td>
</tr>
<tr>
<td>DHS</td>
<td>Demographic and Health Surveys</td>
<td>Large-scale national household surveys following a standard format to collect data on demographic and health variables.</td>
</tr>
<tr>
<td>EPI</td>
<td>Expanded Programme on Immunization</td>
<td>A programme initiated by WHO in 1974 for immunization of children against six diseases (tuberculosis, polio, diphtheria, pertussis, tetanus, measles). Adopted by almost all LMC.</td>
</tr>
<tr>
<td>GNI</td>
<td>Gross National Income</td>
<td>The income from the production of all goods and services produced in a country in a specified time period.</td>
</tr>
<tr>
<td>HDI</td>
<td>Human Development Index</td>
<td>A composite index based on indicators of standard of living, education and health in a defined population.</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency virus</td>
<td>The virus that causes AIDS.</td>
</tr>
<tr>
<td>ICDDR, B</td>
<td>International Centre for Diarrhoeal Diseases Research, Bangladesh</td>
<td>A large international research centre in Dhaka, Bangladesh which was established as the Cholera Research Laboratory 1960 and expanded and given its current name in 1978.</td>
</tr>
<tr>
<td>IMCI</td>
<td>Integrated Management of Childhood Illness</td>
<td>A model for examining, diagnosing and treating children less than five years old that suffer from acute infections.</td>
</tr>
<tr>
<td>KI</td>
<td>Karolinska Institutet</td>
<td>Karolinska Medical University, Stockholm, Sweden</td>
</tr>
<tr>
<td>LFA</td>
<td>Logical Framework Approach</td>
<td>A model for planning, implementing and evaluating activities or programmes.</td>
</tr>
<tr>
<td>LMC</td>
<td>Low- and Middle-Income Countries</td>
<td>Countries with low to middle GNI (countries listed in Annex 1).</td>
</tr>
<tr>
<td>ORS</td>
<td>Oral Rehydration Salts</td>
<td>A prefabricated package of a powder containing glucose and sodium, and often also a base like trisodium citrate, and potassium. The powder is to be mixed in water and used for rehydration.</td>
</tr>
<tr>
<td>ORT</td>
<td>Oral Rehydration Therapy</td>
<td>Oral treatment of dehydration with a recommended rehydration fluid.</td>
</tr>
<tr>
<td>MDDA</td>
<td>Sistema de Monitoração de Doenças Diarréicas Agudas</td>
<td>A system established in Brazil for weekly reporting on number of diarrhoea cases coming to health services.</td>
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<tr>
<td>Acronym</td>
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<tr>
<td>MDG</td>
<td>Millennium Development Goals</td>
<td>Goals for human development set for 2015 by the UN.</td>
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<tr>
<td>MOH</td>
<td>Ministry of Health</td>
<td></td>
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<tr>
<td>NE</td>
<td>Northeastern</td>
<td>In this thesis used in connection with Northeastern Brazil, a region comprising nine states in Brazil.</td>
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<tr>
<td>NGO</td>
<td>Non-governmental organisation</td>
<td>An organisation with no formal organisational links to the government</td>
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<tr>
<td>P</td>
<td>Probability</td>
<td></td>
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<tr>
<td>PACS</td>
<td>Programa Agentes Comunitários Saúde</td>
<td>A community outreach programme in Brazil.</td>
</tr>
<tr>
<td>PSF</td>
<td>Programa Saúde de Família</td>
<td>A community outreach programme in Brazil targeting families and providing essential family health services.</td>
</tr>
<tr>
<td>RHF</td>
<td>Recommended Home Fluids</td>
<td>Fluids recommended by a ministry of health or another leading agency for use when a child suffers from diarrhoea.</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
<td>A statistical measure of the spread of variable values.</td>
</tr>
<tr>
<td>SIAB</td>
<td>Sistema de Informação da Atenção Básica</td>
<td>A reporting system based on information from community health workers (PSF/PACS) in Brazil.</td>
</tr>
<tr>
<td>SIH</td>
<td>Sistema de Informação Hospitalar</td>
<td>The official hospital information system in Brazil.</td>
</tr>
<tr>
<td>SSS</td>
<td>Salt-and-sugar solutions (or sugar-salt solutions)</td>
<td>A fluid prepared by mixing sugar and salt in water.</td>
</tr>
<tr>
<td>UN</td>
<td>United Nations</td>
<td></td>
</tr>
<tr>
<td>UNAIDS</td>
<td>Joint United Nations Programme on HIV/AIDS</td>
<td>The UN programme on HIV/AIDS. UNAIDS brings together the efforts and resources of ten UN system organizations to the global AIDS response</td>
</tr>
<tr>
<td>UNDP</td>
<td>United Nations Development Programme</td>
<td>A UN agency with the task to support development.</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
<td>A UN agency with the task to support children and children’s development.</td>
</tr>
<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
<td>The US government agency responsible for United States’ international aid and development assistance.</td>
</tr>
<tr>
<td>WB</td>
<td>The World Bank</td>
<td>An international organisation made up by two development institutions – The international Bank for Reconstruction and Development (IBRD) and The International Development Association (IDA). Together they provide low-interest loans, interest-free credit, grants and technical advice to LMC for development.</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
<td>The directing and coordinating authority for health within the United Nations system.</td>
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Was it coincidence or destiny? It seemed like coincidence. 1981: I was a fresh graduate of medicine from the Karolinska Institutet (KI) with a strong desire to work in international health and make a contribution to the development of poor nations and people. Through Professor Bo Lindblad at St. Göran’s Children’s Hospital I got an opportunity to spend some time at the Department of Pediatrics at Mayo Hospital, King Edward Medical College in Lahore, Pakistan. The department housed a training centre for diarrhoeal diseases for the Eastern Mediterranean Region of WHO. I was allowed to join one of the courses and less than two months after finishing the undergraduate course in pediatrics at KI I was attending a WHO Regional Training Course on diarrhoea for senior pediatricians. Destiny?

Back in Sweden, I aspired to become a specialist in infectious diseases. 1984: WHO looked for Associate Professional Officers to work with the Programme for Control of Diarrhoeal Diseases (CDD). I had skills and a diploma to show from the course in Lahore. I applied and was recruited to work with the national CDD programme manager, Colonel Akram, in Pakistan in establishing a national programme for diarrhoea control. In early January 1985, I took off from the airport in Örebro to WHO, Geneva. I looked out of the window and waved goodbye to my family – my wife Birgitta and my daughter Anna - standing there alone in the snow at an empty airport. The start of a long journey – that I am still on … and Birgitta and Anna have since been joined by my son Jens in their waving. From many places.

After having served in Pakistan I was recruited in 1986 by Michael Merson and Jim Tulloch at the CDD Programme at WHO, Geneva to work as Evaluation Officer in the programme. During three years I worked intensely on developing evaluation tools and testing them with national counterparts on three continents. I was responsible for the development of a CDD manual on assessing diarrhoea case management in households. I first tested it with colleagues in the Philippines and in Sudan. I then worked in Brazil with the third test of the methodology together with Cesar Victora and Fernando Barros. At the same time we also conducted a health facility survey. It was Cesar and Fernando that engaged me in publishing some of the findings from the studies in NE Brazil (Paper I & Paper II in this thesis).

1989: Back to Sweden. My focus was on public health and I became a specialist in social medicine at the Department of Social Medicine in Stockholm. The intense work with household surveys as CDD evaluation officer from 1986 to 1989 led to an interest in methodological issues around survey techniques. One result of that interest was a study seeking to assess validity of data on diarrhoea case management in household surveys (Paper III). In 1994 I took a Medicine Licentiate degree at Karolinska Institutet based on my work with household surveys.

My first period with diarrhoea control was one in which focus was on the establishment and dissemination of improved diarrhoea case management, especially oral rehydration therapy (ORT). There was momentum in global efforts to reduce deaths from diarrhoea. Later, data came out that suggested significant successes from these efforts. Case management improved in many countries and diarrhoea mortality subsequently
declined. At the same time, diarrhoea morbidity was reported to change little. Some ten years later, this again triggered my interest in diarrhoea and the relations between morbidity, case management and mortality. The experience over time I had gained with diarrhoea control gave a useful perspective. My earlier work with data from Demographic and Health Surveys (DHS) proved valuable. It was the basis for a study in which data from such surveys were compared over a longer time period to seek better understanding of actual developments of diarrhoeal diseases control over the last 20 years (Paper IV). Then, in 2005 I returned to Brazil after 16 years to study diarrhoea morbidity development in the state of Ceará together with Brazilian colleagues (Paper V).

This thesis is the ultimate proof that diarrhoea has become “the disease of my life”. Was it coincidence? One day, many years after my take-off from Örebro, I was going through documents left behind by my father; the man who contributed so much to my drive to explore the world – its flowers, birds, butterflies, people – and to love it! Among the papers I found a family history that had been compiled by my uncle Erik some years before his death. When reading it I found that my great great grandfather Jes Petersen had died from cholera in Copenhagen on July 19, 1853! One year younger than I am today he was laid to rest – but not in the sacred soil of the cemetery. Outside, because of his contagious and feared disease. Never had I known.

So, I ask again: Was it destiny that I came to work on diarrhoea control? Maybe a man had returned through me to deal with the evils that once took his life? If so, I have served him to the best of my ability. Here is the result – so far …
1 BACKGROUND

The world is divided – one third of the population is sitting on the bulk of the world wealth. Another third is struggling to become wealthier and reach the standards of the richest. A last third is struggling to survive. Poverty is still a reality in many, many households in the world. An estimated 1.1 billion people live in extreme poverty (WB, 2006). Basic amenities are still a luxury to many. Around one billion people in low- and middle-income countries have inadequate access to water and 2.6 billion lack basic sanitation (Shah, 2007). Diseases of poverty, most notably communicable diseases, continue to plague the destitute. Ten to eleven million children die before the age of five in low- and middle-income countries (LMC) (Black et al., 2003), most of them from preventable communicable diseases like diarrhoea.

To rectify this situation the world community has defined global development goals for 2015. This thesis relates to three of those so called Millennium Development Goals (MDG) namely goal number 1: “Eradicate extreme poverty and hunger”, goal number 4: “Reduce child mortality” and goal number 7: “Ensure environmental sustainability” (UN, 2005).

It is in this context of a divided world with poverty related diseases and ambitious goals to fight them that this thesis should be read. Its focus is on diarrhoeal diseases, diseases that have been shown to be possible to control in well-off countries while they still pose a prominent public health threat in low- and middle-income countries.

1.1 Definition, Etiology and Treatment of Diarrhoeal Diseases

Diarrhoea is defined in medicine as the passing per day of three or more stools that are sufficiently liquid to take the shape of a container (Keusch et al., 2006). Diarrhoea have many causes, the most common being intestinal infection. Common etiological agents are bacteria like escherichia coli, campylobacter, salmonella and shigella bio-serotypes or viruses like adenovirus, rotavirus and norwalkvirus. Parasites like entamoeba histolytica and giardia lamblia also cause diarrhoea (Merson et al., 2005).

The best known and most feared form of diarrhoea is cholera, caused by vibrio cholera, a gram-negative bacterium. In its worst form it causes profuse diarrhoea with stools like rice-water. The resulting fluid loss can quickly lead to death when untreated (Ryan & Calderwood, 2000).

Dysentery signifies passing of stools with blood. It was a feared disease before the advent of antibiotics, not least in wars when epidemics could kill large numbers of soldiers and civilians. It is still endemic in many countries and at times causes epidemics. The most common causes of dysentery are shigella and amoebiasis (Pazhani et al., 2004; Keusch et al., 2006).

Determining etiology of diarrhoea episode is often difficult, even under controlled conditions. The pathogen causing the disease may not be found in as many as half of the cases presenting at a modern hospital with good diagnostic facilities (Klein et al., 2006).
The most common complication of diarrhoea is dehydration due to loss of fluids. In the early stages dehydration leads to thirst and irritability, in the later stages collapse of essential body functions and ultimately death (Merson et al., 2005). Due to the importance of treating dehydration early it has proven rational to classify acute watery diarrhoea into cases without signs of dehydration, with some dehydration and with severe dehydration (WHO, 2005). The standard approach to treatment is to give a case without signs of dehydration plenty to drink to prevent development of dehydration and a case with some dehydration oral rehydration with specific fluids containing glucose and sodium. Cases with severe dehydration are best treated with intravenous fluids in the acute stage as restoration of the fluid balance is urgent (Mahalanabis et al., 1972; Merson, 1983; WHO, 2005).

Antibiotics should be given in cases of cholera (Behrens, 1991) and dysentery (Fontaine, 1988; Dutta et al., 2003). For other infectious causes of diarrhoea in children, antibiotics are not generally recommended (WHO, 2005).

Anti-motility drugs and other anti-diarrhoeal drugs are not recommended in the treatment of childhood diarrhoea due to their limited effect on short-term diarrhoea, their potential side-effects and the risk of over-dosage (Richards et al., 1993; WHO, 2005).

Zinc has been found to reduce the severity and duration of the illness episode and also lower the incidence of diarrhoea in the following 2-3 months (Bhutta et al., 1999; WHO, 2005). It is now recommended that all children with diarrhoea be given zinc as early as possible in a diarrhoea episode (Fontaine, 2001).

Persistent or chronic diarrhoea is a condition with high fatality (Fauveau et al., 1992). The primary treatment of persistent diarrhoea is correction of malnutrition and prevention of complications related to malnutrition (Fontaine et al., 1985).

New treatments of diarrhoea are constantly being explored. At Karolinska Institutet researchers are investigating the role of lactobodies in diarrhoea treatment (Pant et al., 2006). A non-profit pharmaceutical company, OneWorld Health, works on the development of safe, effective and affordable anti-secretory drugs for adjunct use with ORT (OneWorld Health, 2007). Gates Foundation supported this work with a grant of US$ 46 million in 2006 (Blankinship, 2006).

1.2 A Global Public Health Problem

Diarrhoeal diseases constitute a major burden of disease in low- and middle-income countries. The incidence in children below five in those countries was estimated at 3.2 episodes per year and child in 2003 (Parashar et al., 2003a). There has been little progress in reducing diarrhoea over the past decade (Kosek et al., 2003). In 1993 the average number of episodes per children was estimated to 3.5 per child and year (Jamison et al., 1993).

A global review of childhood mortality presented in Lancet in 2003 showed that diarrhoea still is a significant cause of childhood deaths (Black et al., 2003). Data in the article illustrates that around 22 % of 10.8 million annual deaths in children less than
five years old are caused by diarrhoea. This would correspond to 2.3 million children. More recent data provide estimates of around 2.0 million child deaths each year in LMC due to diarrhoea (Bryce et al., 2005a). In 1982 the estimate was 4.6 million child deaths (Snyder & Merson, 1982).

Diarrhoea is estimated to account for 12% of all deaths due to infectious diseases in the world (Figure 1). Around 90% of these cases occur in children in LMC (Kallander, 2007).

![Figure 1](image)

**Figure 1.** Distribution of deaths due to infectious diseases in the world. Estimated annual number of deaths 15 million. (Source: Kallander, 2007)

### 1.3 Framework

Human being is constantly exposed to potentially infectious organisms. The struggle to combat these organisms is a continuous and life-long process. The defence against microbes and germs is a vital and essential function in survival. Its outcome depends on many factors. They can be clustered into host factors, agent factors and environmental factors (Last, 1980) (Figure 2).
1.3.1 Host Factors

Host factors are factors that relate to the person hosting the infectious agent. The most important host factor is the immune system. Its strength depends on factors like genetics and the physical and mental state of the patient. The latter depends among other things on nutrition, rest and stress. It has been documented that malnutrition increases the risk of dying from diarrhoea (Ochoa et al., 2004). Stress has been found to have a direct effect on the immune function through impairment of natural killer cell cytotoxicity (Cohen et al., 2007). Stress is constant in many poor families in LMC.

The inclination to contract disease will depend on the degree to which the individual has been exposed to agents enabling him or her to develop immunity. This is important in “traveller’s diarrhoea” in which persons visiting tropical countries contract diarrhoea if they have not been exposed before to common diarrhoea pathogens in these countries, preventing them from developing immunity against these organisms (Steffen et al., 1983; DuPont & Ericsson, 1993; Wittesjo et al., 1995).

The importance of the immunological system in the protection against diarrhoea is illustrated in HIV infection in which the immunological system is defunct. Diarrhoea is one of the first clinical manifestations of AIDS (Keusch et al., 1992).

The defence against diarrhoea agents also depends on the micro-environment in the gastro-intestinal tract. Many germs are for instance killed already in the ventricle by hydrochloric acid. People with low levels of such gastric acid (achydia) are more prone to contract diarrhoea than others.

The host defence can be strengthened by immunisation. Vaccines with high effectiveness against diarrhoeal diseases have generally been difficult to develop. It took
a long time to produce a rotavirus vaccine that is sufficiently efficient to be recommended for general use (Dennehy, 2005). In 2006, Brazil could as one of the first countries in the world include immunization against rotavirus in their national immunization programme (MOH, 2006). Cholera has long been a target for vaccine development. Progress in research on vaccines has been made over the years (Ryan & Calderwood, 2000) but the efficacy of existing cholera vaccines is still not satisfactory (Calain et al., 2004).

Immunisation against measles has proven to be important for reducing diarrhoea morbidity and mortality as diarrhoea is a common complication of measles (Feachem & Koblinsky, 1983).

1.3.2 Agent Factors

Agent factors of importance to the occurrence and outcome of diarrhoea are virulence of the agent, pathophysiology and dose and frequency of exposure.

Virulence is the relative ability of an organism to cause disease. Many microbes causing diarrhoeal diseases generally have medium to low virulence, i.e. medium to high doses of pathogens are required to cause disease. Shigella is an exception – few bacteria are required to cause symptomatic disease (Kotloff et al., 1999). Cholera on the other hand requires high concentration of the bacteria to cause infection in healthy individuals (Ryan & Calderwood, 2000).

Most viruses tend to cause mild to moderate diarrhoea but they can also be lethal, especially in infants (Merson et al., 2005). Rotavirus and norwalk virus are highly virulent and occur in epidemics. Rotavirus is a known cause of diarrhoea outbreaks among infants in hospitals (Rodrigues et al., 2007).

Bacteria causing diarrhoea primarily act through two pathophysiological mechanisms. One is through the release of toxins that affect the secretion or absorption of fluids in the intestine, another is through invasion of the mucous membranes, usually of the large bowel. Cholera for instance releases a toxin that induces profuse and unlimited secretion of fluids (Behrens, 1991). Shigella on the other hand invades and damages the mucosa of the large bowel and causes loss of both fluids and blood.

Viruses that cause diarrhoea often infect the small cells of the intestinal villi. This leads to malabsorption by impaired hydrolysis of carbohydrates and excessive fluid loss (Keusch et al., 2006).

The frequency of exposure from diarrhoeal agents is a function both of specific agent factors and the environment. Characteristics of the agent that matter is for instance the ability of the agent to survive outside the human body. Shigella is very sensitive and expires quickly in the environment. Cholera survives well in water and sewage. Many diarrhoea agents thrive in organic material and can therefore multiply rapidly in food. All these various characteristics are important for control measures. In shigella, isolation of the individual is particularly important. In cholera it is important to reduce the contacts between the infected and others, but it is equally important to limit the use of water sources containing the vibrios (Behrens, 1991). Control of hygiene in public
eating places is a well established public health function to prevent the occurrence and spread of pathogens like salmonella and escherichia coli.

### 1.3.3 Environmental Factors

The impact on diarrhoea from socio-economic development is mediated through a number of factors. Mosley and Chen (1984) made a distinction between distal (underlying) and proximal determinants in relation to health improvements. Distal determinants are for instance socioeconomic conditions, culture and ecology. They affect morbidity and mortality through so called proximal determinants like family formations, household environment including sanitary facilities and availability of safe water and food, attitudes and policies in the society, and collective or individual behaviour. Those factors are often interrelated (Scholthof, 2007).

#### Water and food

The most important factors with direct impact on diarrhoeal diseases are clean water and safe food (Feachem, 1986). Lack of safe water and proper sanitation in combination with poor hygiene may cause as much as 90% of all childhood diarrhoea in low- and middle-income countries (WHO, 1997). A model of the interaction between water and diarrhoea (the “F-diagram”) distinguishes five pathways of transmission: within households, household-to-household, household-to-water, water-to-household, external-to-community (Huttly et al., 1997; Eisenberg et al., 2007). The most common route of transmission of diarrhoeal agents is the faecal-oral route, within households or between households (Keusch et al., 2006). Agents are excreted through faeces by carriers and transmitted to other persons either through water, food or personal contact. Hand washing after having passed stools is particularly important as a measure at individual level to reduce spread of pathogens (Huttly et al., 1997; Clasen et al., 2006). Provision of safe water, proper sanitation, waste management and food control are vital community interventions to prevent diarrhoea.

#### Other factors

Other environmental factors of relevance to the occurrence of diarrhoea are traditional beliefs and cultures (Ellis et al., 2007), the health care system (Mills et al., 2006), the role and status of women (Rihani, 2006) and the society at large (Scholthof, 2007). Socio-economic differences matter since many of the risk factors are associated with poor socio-economic conditions (Burstrom et al., 2005). Diarrhoeal diseases are very much diseases of poverty and the poor (Gwatkin et al., 1999; Wagstaff et al., 2004). Climate and seasonal variation in temperature is also important to the occurrence of diarrhoea (Mahmud et al., 1993; El-Gilany & Hammad, 2005). Bacteria thrive in higher temperatures while rotavirus spreads more easily during winter (Rendi-Wagner et al., 2006).
The health system

A reception area, some beds, good hygiene and knowledge and skills on how to administer ORT and intravenous therapy are the basic requirements for successful management of diarrhoea cases (Mahalanabis et al., 1973). However, both the infrastructure and the skills may be deficient due to system problems (WER, 1993; WHO, 1994; Bryce et al., 2004; Rowe et al., 2005). Knowledge on correct management of diarrhoea may be inadequate and equipment missing. This may contribute to underutilization of oral rehydration (Hong et al., 2003) and excessive prescription of drugs with no or at worst harmful effects (Bojalil & Calva, 1994; Haak & Claeson, 1996).

A well function disease control programme will depend on a strong health system with facilities and well trained and motivated personnel in place (Lindstrom et al., 2006). A particularly challenge in diarrhoea control lies in the fact that a large number of children are taken to private providers for care (Bustreo et al., 2003; Waters et al., 2003) where the quality of services vary (Das et al., 2005). Private providers are often difficult to reach through public health programmes (Kamat, 2001). Also, many caretakers in low- and middle-income countries go directly to pharmacies and drug vendors, who become a major source of advice and dispensing in childhood diarrhoea (Raghu et al., 1995; Sur et al., 2004; Larson et al., 2006). Market forces influence both providers of care and drug vendors, a fact that gives the pharmaceutical industry an important role in diarrhoeal diseases and their management. The industry is the key actor in developing and promoting drugs for diarrhoea.

1.3.4 Interventions to Reduce Diarrhoea Morbidity and Mortality

Disability and death are two major outcomes to consider when assessing the public health impact from diarrhoeal diseases (Lopez et al., 2006). Disability is a function of morbidity. The two outcomes can be measured in loss of years due to death or disability (Murray, 1994), loss of quality of life (Sassi, 2006) or in loss of income to the community and the household (Evans & Jamison, 1994; Evans et al., 2005).

Measures to control diarrhoeal diseases should aim at reducing morbidity, and thereby disability, and mortality. Mortality changes are a result of changes in incidence, changes in case-fatality rate or changes in both.

Important interventions to reduce incidence of diarrhoea are provision of safe water (Moraes et al., 2003; Fewtrell & Colford, 2005; Clasen et al., 2006), improved sanitary facilities (Moraes, et al., 2003), and promotion of personal and domestic hygiene (Huttly et al., 1997). Those interventions all aim at breaking the faecal-oral route of transmission. Interventions to strengthen immunity are vaccination against rotavirus (Parashar et al., 2003b; Dennehy, 2005) and measles immunization (Feachem & Koblinsky, 1983).
Interventions to reduce case-fatality aim at strengthening the immune defence or improving case management\(^1\). Promotion of exclusive breastfeeding (Barros et al., 1995; Haider et al., 1996) and improved complementary feeding practices (Victora et al., 1999; Jones et al., 2003) fall in the first category. Case management interventions are increased amounts of fluids and continued feeding from the onset of diarrhoea, referral if the illness gets worse, treatment with specific rehydration fluids like ORS, in cases with some dehydration, intravenous therapy for severe dehydration, zinc supplementation, treatment with antibiotics in cholera and dysentery, and nutritional rehabilitation of persistent diarrhoea (WHO, 2005).

1.4 Development of Control of Diarrhoeal Diseases

1.4.1 The Early Years

Control of diarrhoeal diseases is in this work defined as systematic public health action to reduce morbidity or mortality from diarrhoea. Efforts to that end goes back to 1854 when John Snow studied a cholera outbreak in London. He was able to show that the disease was associated with use of water from a particular community well, The Broad Street Pump (Newsom, 2006). Snow’s work created awareness of links between unclean water and cholera resulting in increased action in cities to keep water free from contamination. Later, processes for treating water for germs were established (Wallace, 1998). With the development of concepts of hygiene and cleanliness by Rudolf Virchow in Berlin at the end of the 19\(^{th}\) century (Brown & Fee, 2006) more systematic and organised community action was made to prevent the spread of diseases, including diarrhoea, in the cities where population density was high (Katajamaki & Suomalainen, 2001; Louis, 2004; Cutler & Miller, 2005). Control of food outlets was also established (Borchers et al., 2007). All this lead to significant health improvements and reductions of diarrhoea mortality (Burstrom et al., 2005; Cutler & Miller, 2005). Techniques for water treatment improved continuously. Hygiene and environment control became important functions in the organisation of society and public health protection was given high priority (Pothisiri, 1997; Moore, 2001). The provision of safe water and proper sanitation improved and eventually reached almost universal coverage in Western Europe and the United States. In LMC, governments continue to expand access to safe water and proper sanitation, trying to keep up with growing populations that need such services (WHO, 1997).

The focus on diarrhoeal diseases control remained relatively unchanged from the late 19\(^{th}\) century to the end of the 1960s. Public health laboratories and researchers worked on diagnosing the causes of diarrhoea, looking for its etiology. This appeared rational as pathogens potentially could cause large epidemics if control measures were not taken early. The introduction of intravenous fluids represented a major change (Vinnars & Wilmore, 2003) in case management. In settings where resources were sufficient the most feared complication from diarrhoea, dehydration, could now be treated with intravenous fluids.

\(^{1}\) By "case management" is in this thesis meant examination, diagnosing, treating and following up of a child with illness (in the thesis most often diarrhoea). The term "management" is used either in this context or in relation to a broader concept or activity, like a programme or an intervention.
1.4.2 Development of Oral Rehydration Therapy (ORT)

In the 1960s researchers at the International Cholera Research Laboratory in Dhaka (later ICCDR, B) found that taking a fluid orally that contained sugar (glucose) and salt (sodium) in certain combinations could enhance absorption of water from the gut (Nalin et al., 1968; Pierce et al., 1968). This was a dramatic discovery. It meant that acute dehydration could be corrected by providing fluids orally instead of intravenously. Oral Rehydration Therapy (ORT) only required water, sugar and salt and could potentially be applied by anyone.

During the war of independence from Pakistan in East Bengal, later Bangladesh, there was a great influx of refugees to Calcutta from East Bengal. In the overcrowded camps cholera broke out with potentially disastrous consequences. The case-fatality rate from untreated cholera has been estimated at 30%. Though ORT still had not been fully established in routine clinical work, it was applied at large scale during the cholera outbreak. This resulted in a dramatic decrease of case-fatality rates down to 3% and many lives were consequently saved (Mahalanabis et al., 1973). A powerful remedy for diarrhoea mortality had thereby been identified and established. ORT was later called the most important scientific discovery in modern times as it had the potential to save millions of lives lost due to diarrhoea (Fontaine et al., 2007).

ORT has often been promoted with the help of distribution of a pre-fabricated package with a powder containing glucose, sodium chloride, a base like trisodium citrate (originally sodium bicarbonate), and potassium chloride. This package and the resulting solution is what is referred to as ORS (Oral Rehydration Salts). For many years, WHO recommended a single formulation of ORS to prevent or treat dehydration, no matter the cause or age of the patient. After significant research seeking to reduce the osmolarity of ORS to avoid possible adverse effects of hypertonicity or hypernatremia in children, WHO decided in 2004 to recommend a new formula for ORS with a sodium content of 75 millimol (mmol)/litre as compared to 90 mmol/litre in the old one (Table 1) (WHO, 2004b). Studies had shown that this formula could reduce the need for intravenous therapy in children with diarrhoea by 33% and that stool output decreased by about 20% and vomiting by about 30% in comparison with the previous ORS formula (Mahalanabis, 1996, Santosham et al., 1996).

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Grams/litre</th>
<th>Mmol/litre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium chloride</td>
<td>2.6</td>
<td>75 (sodium alone)</td>
</tr>
<tr>
<td>Glucose, anhydrous</td>
<td>13.5</td>
<td>75</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>1.5</td>
<td>20 (potassium alone)</td>
</tr>
<tr>
<td>Chloride</td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>Trisodium citrate, dehydrate</td>
<td>2.9</td>
<td>10 (citrate)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>20.5</strong></td>
<td><strong>245</strong></td>
</tr>
</tbody>
</table>

Table 1. Current WHO recommendation on composition of ORS
1.4.3 A Global Programme for Control of Diarrhoeal Diseases (CDD)

Knowledge on ORT disseminated slowly and the introduction of a simple solution to a life-threatening condition, dehydration, did not easily catch on in the medical community. This, in combination with the potential importance of the solution in lowering child mortality, was the rationale behind establishing a global programme to reduce morbidity and mortality from diarrhoeal diseases. In 1980, the World Health Organization initiated The Programme for Control of Diarrhoeal Diseases in children (CDD). The programme made reduction of child mortality due to diarrhoea its immediate objective and a decrease in diarrhoea morbidity a longer-term objective (Merson, 1983). The primary intervention chosen to reduce diarrhoeal mortality was promotion of ORT. It was estimated by the WHO CDD programme that about two thirds of all diarrhoeal deaths in children were due to acute watery diarrhoea and hence could be prevented with ORT (WHO, 1984).

The CDD programme selected clear strategies to control diarrhoea: proper case management, promotion of proper nutrition, promotion of proper hygiene and provision of ample quantities of safe water (WHO, 1984). Largely, however, the focus of the programme was on case management. Technical material was produced, including a treatment algorithm for examining and treating a child with diarrhoea. Major efforts were put into training of health workers and education of caretakers. The programme primarily worked through government health services. To reach the private sector and consumers, social marketing of key messages directly to the public was promoted and practiced in national CDD programmes (WHO, 1989b; WHO, 1994; Miller & Hirschhorn, 1995).

WHO was consistent in seeking to base diarrhoea control policies and recommendations on evidence. As such it could be seen as a role model for WHO’s work, a model that has recently been called for by Oxman et al. (2007). The programme supported a large research programme in the 1980s (WHO, 1999a) which included studies of a number of interventions potentially important for reduction of diarrhoea morbidity and mortality, like promotion of breastfeeding, female education, and measles immunization (Feachem, 1986). The result of the research formed the basis for WHO’s recommendations on prevention of diarrhoea.

Initially, WHO recommended countries to set targets for diarrhoea morbidity and mortality reduction (WHO, 1984), but later it revised these targets to reflect to what extent case management was properly carried out (WHO, 1993). Indicators of case management included rehydration and feeding during diarrhoea, and when required correct antibiotic. Indicators for training coverage were also developed and included in programme monitoring.

The CDD programme advised countries to develop National CDD programmes with a specific plan and a programme manager at ministry level. It developed special training manuals and encouraged training of national programme managers and mid-level managers in planning and implementation of CDD programmes. The mid-level managers were usually province, district or hospital managers and they were typically in charge of several other activities or control programmes.
More than one hundred national programmes for diarrhoeal diseases control were established from 1980 to 1990 (WHO, 1989b). Promotion of ORT was very active during those years, globally through WHO and nationally through ministries of health with support from UNICEF, WHO and donors (USAID, 1983; USAID, 1985; USAID, 1988).

1.4.4 New issues – Disease Control and Health Systems

The implementation model used for diarrhoeal diseases control by WHO was largely based on a Logical Framework Approach (LFA) and adopted from the Expanded Programme on Immunization (Henderson, 1984; WHO, 1984). The model has clear objectives, targets and activity plans. It has over the years been applied to many other disease control programmes, including most recently HIV/AIDS (Gilks et al., 2006). It is a public health model which is characterized by a focus on one disease, clear targets and simple interventions. Priority is given to common cases rather than unusual or rare cases as is often done in school medicine. This disease control model has been associated with “vertical interventions” rather than systemic or “integrated” approaches (Walsh & Warren, 1979; Rifkin & Walt, 1986; Forsberg, 2001). The debate has been lively on whether or not health is best promoted in a longer perspective by broad system support and development, or by specific targeted programmes that seek immediate gains in reduction of morbidity and mortality (Kendall, 1988; Unger et al., 2003; Unger et al., 2006a,b). To study diarrhoeal diseases control as designed and promoted by WHO is of considerable interest to this public health debate and to the general question on how health can best be promoted in a sustainable way. The need for health systems research to improve child survival was recently highlighted in a survey presented in Lancet very recently (Costello et al., 2007).

1.4.5 New Issues - Integrated Management of Childhood Illness (IMCI)

From the mid-nineties a new approach to child health care was adopted. It was called Integrated Management of Childhood Illness (IMCI) (Tulloch, 1999). The basis for the IMCI was that a child that is ill often suffers from several conditions at the same time. Also, a child will show up with symptoms that may be associated with several disorders (Kallander et al., 2004). Hence, health workers should be trained to assess the child in general for a number of symptoms that may lead to one or several diagnosis. Up to the development of IMCI assessment and treatment algorithms, WHO had been working on one algorithm for acute respiratory tract infections (ARI), one for diarrhoea, one for malaria, etc. With the IMCI all these algorithms and several more, including nutritional assessment (Campbell & Gove, 1996), were merged into one major (Gove, 1997). Programmatic efforts have been made since the mid-90s to promote this algorithm (Bryce et al., 2005b).
1.4.6 Impact of CDD in Low- and Middle-income Countries

The global impact of programmatic control of diarrhoeal diseases from 1980 onwards has been assessed in a limited number of studies (Claeson & Merson, 1990; Bern et al., 1992; Victora et al., 2000). In a review carried out by Victora et al. (2000) positive trends in diarrhoea management was seen in most parts of the world. The study suggested that oral rehydration was given to the majority of children with diarrhoea at the end of the 20th century. As a result, it was estimated in the study that the annual number of deaths attributable to diarrhoea among children below 5 years fell from around 4.6 million in 1980 to about 1.5 million in the year 2000. These estimates of mortality reduction from ORT were indirect, measured through the adoption of control measures and their assumed life saving effect.

Thorough studies at country level of large-scale impact from diarrhoeal diseases control activities are limited. An evaluation of the National Programme for Control of Diarrhoeal Diseases in Egypt showed a decrease in mortality with the implementation of the programme (Miller & Hirschhorn, 1995). The programme gave priority to promotion of ORS packets through social marketing.

In Brazil, a study of nine states in the northeast showed a reduction in mortality from 1980 to 1989. The authors controlled for factors that could have influenced diarrhoea morbidity and case fatality and found that the reduction seemed to be linked to increased use of rehydration therapy (Victora et al., 1996).

In Mexico, a study of diarrhoea mortality from 1978 to 1993 showed that the proportion of deaths caused by diarrhoea among children under five dropped from 25% in 1978 to 11% in 1990 (Gutierrez et al., 1996). In this study the strongest correlation occurred between improvements in water and sanitation and diarrhoea mortality reduction, followed by increase of ORT use rates and mortality decline. Other factors, which were found to have a positive impact on death rates attributable to diarrhoea, were female literacy and measles vaccination.

In the Philippines, a national evaluation of the diarrhoea control programme showed positive achievements in programme implementation, achievements that could have contributed to substantial observed reductions in diarrhoea morbidity and mortality. However, changes in other relevant factors and lack of correlation at the ecological level argued for caution in establishing a causal connection (Victora et al., 2000).

In summary, research so far indicates that diarrhoeal diseases control programmes have had an impact in the countries under study. The studies also point to methodological problems in such impact evaluations. The sources of errors are multiple so caution should be exerted when generalizing findings. Also, a bias towards publishing positive findings in the literature must be considered. A desire to look for results supporting the cost effectiveness of the systematic interventions undertaken cannot be excluded.
2 RATIONALE FOR THE RESEARCH AND AIM OF THE THESIS

2.1 Rationale

From a review of existing knowledge on diarrhoeal diseases and its development the following rational reasons for the research have been identified.

The first is the need for further studies on effects and impact from disease control programmes. Few studies have been carried out to assess the impact of significant programme investments in a global programme which was implemented in more than 100 countries and which up to 1992 had generated production of more than 800 million packets of ORS in developing countries (WHO, 1999a). Since, the use of ORT has been widely adopted. ORS packets are now available in many health facilities and drug outlets in low- and middle-income countries. There is therefore a great need to carry out studies in communities where environment and data availability allow systematic studies of developments of diarrhoea interventions and their impact.

The second is the need for further studies on the development of diarrhoea morbidity and its determinants. The impact on diarrhoea from socio-economic development is mediated through a number of factors as described above (Mosley & Chen, 1984). Progress has been made in many of those determinants over the past decades. For instance, an estimated 816 million persons gained access to water and 747 million to proper sanitation from 1990 to 2000 (WHO, 2000). Measles immunization coverage has also improved (WHO, 2006a; Elliman & Bedford, 2007). Still, there is limited understanding of the relation in real settings between these determinants and diarrhoea morbidity and mortality (Zwane & Kremer, 2007). This knowledge is of particular interest to countries that are now moving from lower to higher income levels. Better understanding can assist those countries in setting priorities and making correct choices to reduce the burden of diarrhoeal diseases.

The third is the opportunity to explore the implementation of diarrhoeal diseases control through available data. Over the years, the number of data sources on diarrhoea indicators has grown. A major source of information is the Demographic and Health Surveys (DHS) Programme (DHS, 2007). DHS surveys are national surveys of demographic and health data. Ideally, they are conducted nationally every five years to measure progress. A standard DHS survey collects information on diarrhoea morbidity, knowledge on diarrhoea management and measures taken when a child in the household develops diarrhoea. Background characteristics of the households, like age, sex, educational level of the caretaker or household head and geographic location of the household, are also collected.

The DHS surveys have been carried out regularly in many countries. By combining DHS results from a large number of countries it is possible to review trends in the indicators for several or all countries surveyed. Such studies using aggregated data can be useful for identifying common patterns that may expand our knowledge on disease control and efforts to improve public health.
The fourth is the need for further methodological development in evaluation. The two most important instruments for evaluating the effects on performance and outcome from case management interventions for diarrheal diseases control are household surveys (WHO, 1989a) and health facility surveys (Forsberg et al., 1992; Bryce et al., 1992). WHO has developed such instruments in close collaboration with national institutions and research organisations. The surveys have focused on assessing to what extent caretakers in the community and health staff follow messages and advice on proper diarrhoea case management and prevention. Diarrhoea mortality will be low if children are taken well care of in their homes, referred if their condition deteriorates and are well treated at health facilities when they get there. The evaluation should therefore assess to what extent those measures are established practice.

Even if significant efforts have been invested in developing household survey tools, there are few studies that have sought to validate them (Kroeger, 1985; Nordberg, 1988; Ferrinho et al., 1995). This may be one reason why they have occasionally generated results of dubious quality (WHO, 1987). Up to now, around 200 DHS surveys in more than 70 countries have been implemented. During the 80s and early 90s more than 400 CDD household surveys were conducted in low- and middle-income countries (WHO, 1994). Household surveys were and are frequently used in programme evaluation (Oyoo et al., 1991; Forsberg, 1994; Bowling, 2005). All this points to the need to critically review the data generated from household surveys and health facility surveys and to seek validation of that data. A continuous development of the tools and the way in which they are applied is essential. This will not only improve our understanding of diarrhoeal diseases and interventions for their control, but also contribute to improvement in public health interventions and evaluation.

2.2 Aim of the thesis

The main aim of this thesis is to make a contribution to improved child health in LMC by enhancing knowledge on diarrhoeal diseases control, especially on case management and morbidity reductions.

The specific objectives of the thesis are to:

- determine diarrhoea case management in households in a setting where significant efforts have been made to improve that management in order to identify programmatic effects, and problems and challenges in diarrhoea management in households, (Paper I)
- determine the quality of diarrhoea case management in primary care in a defined setting in order to identify programmatic effects, and problems and challenges in diarrhoea management in primary care implementation, (Paper II)
- analyse the quality of household surveys in determining diarrhoea case management in households and identify potential areas for improvement in survey implementation, (Paper III)
- review progress of diarrhoea case management in low- and middle-income countries to assess the impact of control activities on diarrhoea case management, (Paper IV)
• analyse developments of diarrhoeal diseases in a setting where diarrhoea is common and relate differences in diarrhoea morbidity to determinants in order to better understand how diarrhoea morbidity can be reduced. (Paper V)
3 METHODS

3.1 Study Design

The design of this research work was developed within the overall framework described above and driven by the key research issues. It was linked to established theory and approaches to programme and intervention evaluation (Wallace, 1998; Rossi et al., 2003; Kirkwood, 2004; Bowling, 2005). The long term perspective allowed for analysis of trends while the field studies provided a base for more detailed research on behaviour and implementation of diarrhoea control.

The design can be seen in relation to the course of a diarrhoea episode. One study looked at morbidity and its determinants (Paper V). Two studies focussed on the illness episode at household level (Paper I & Paper IV). One was specifically addressing the methodology for assessing the action taken in the households (Paper III). Lastly, one study looked into the quality of services offered in health facilities where those children are received that do not recover at home (Paper II).

The first study in this project made use of household surveys for evaluating diarrhoea case management in NE Brazil. The second study assessed quality of care using health facility surveys as instrument. In the third work a statistical and epidemiological comparison was made of data from household surveys specifically made of diarrhoeal diseases and data from DHS surveys. In the fourth study the development of diarrhoea management across countries over a longer time period was analysed using data from DHS surveys in LMC. In the fifth, a more elaborate assessment of the development of diarrhoea morbidity was made in a confined setting. The study investigated if diarrhoea morbidity differences were associated with differences in diarrhoea morbidity determinants. The study design is summarized by study in Table 2.

My perspective of having worked with diarrhoeal diseases control in the mid-80s when enthusiasm for ORT was possibly at its peak, over the introduction of IMCI, the launch of large-scale health funds for other communicable diseases than diarrhoea (Feachem & Sabot, 2006), and eventually the current period of renewed interest in child health (Lancet, 2007) and child health research (Costello et al., 2007) should bring an added value to the research and the analysis.
<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Study object/population</th>
<th>Study Methods</th>
<th>Study Period</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Management of childhood diarrhoea at the household level: a population-based survey in NE Brazil</td>
<td>Determine diarrhoea case management in households</td>
<td>The population in NE Brazil</td>
<td>Household survey</td>
<td>1989</td>
<td>Frequency distribution with confidence intervals</td>
</tr>
<tr>
<td>II. Quality assurance of a diarrhoea control programme in NE Brazil</td>
<td>Determine the quality of diarrhoea case management in primary health services</td>
<td>Health facilities and health workers in NE Brazil</td>
<td>Health facility survey</td>
<td>1989</td>
<td>Frequency distribution with confidence intervals</td>
</tr>
<tr>
<td>III. Cross-sectional household surveys of diarrhoeal diseases – a comparison of data from CDD and DHS programmes</td>
<td>Analyse the quality of household surveys in determining diarrhoea case management practices in households</td>
<td>Nine pairs of household surveys from eight countries</td>
<td>Analysis of data from household surveys</td>
<td>1991-93</td>
<td>Chi square test, Spearman rank correlation</td>
</tr>
<tr>
<td>IV. Diarrhoea case management in low- and middle-income countries – an unfinished agenda</td>
<td>Review progress of diarrhoea case management in low- and middle-income countries</td>
<td>107 household surveys from 40 countries</td>
<td>Analysis of data from household surveys</td>
<td>2005-2006</td>
<td>Trend analysis using random coefficient regression and linear modeling</td>
</tr>
<tr>
<td>V. Why so little change in diarrhoea morbidity in low- and middle-income countries? – A study from Brazil</td>
<td>Analyse developments of diarrhoeal diseases in a confined setting. Relate differentials in diarrhoea morbidity to determinants.</td>
<td>Population of the state of Ceará in NE Brazil</td>
<td>Analysis of data from routine reporting and population census.</td>
<td>2005-2006</td>
<td>Linear regression analysis of morbidity trends. Linear correlation coefficient analysis of association between determinants and morbidity.</td>
</tr>
</tbody>
</table>
3.2 Research Settings

The thesis is based on data from populations in low- and middle-income countries, Northeastern Brazil and the state of Ceará. The setting in Brazil is part of the larger setting of low- and middle-income countries. Table 3 summarizes some key indicators of the three research settings.

Table 3. Key indicators of the three regions studied in the thesis.

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Population (in millions)</td>
<td>5 238 533</td>
<td>51</td>
<td>8</td>
</tr>
<tr>
<td>GNI/capita (US$)</td>
<td>1 255</td>
<td>1 570</td>
<td>1 329</td>
</tr>
<tr>
<td>Urbanization rate</td>
<td>42</td>
<td>71</td>
<td>76</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>62</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td>Infant mortality rate</td>
<td>57</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>Infant mortality rate 1989</td>
<td>71</td>
<td>78</td>
<td>74</td>
</tr>
</tbody>
</table>

(UNICEF, 2007; MOH, 2006; IBGE, 2006.)

3.2.1 Low- and Middle-income Countries

Low- and middle-income countries (also called developing countries) as defined by the UN are 154 in number (Annex 1) (UNICEF, 2006). Their total population is estimated at 5 238 million and the number of children under five years of age at 553 million. Gross National Income per capita varies from US$ 90 in Ethiopia to US$ 6 230 in Mexico. Life expectancy at birth is 62 years but varies from 33 in Zambia and Zimbabwe to 73 in Sri Lanka. The countries represent a wide variety of socio-economic conditions and cultures. Still, they share some characteristics. One of them is that they have large poor populations, another that infectious diseases still represent a large share of their burden of disease (Gwatkin et al., 1999; Ezzati et al., 2002, Keusch et al., 2006). Infant mortality rates are still on the high side in most of the countries, varying from 13 (Sri Lanka) to 166 (Sierra Leone) per 1 000 children born alive. There is a large variation in the group and the gap between them has widened. It is in fact becoming less meaningful to lump them together. Many countries in Asia have developed well while others, especially in sub-Saharan Africa, have made little to no progress. Out of the 25 countries with the least proportional decrease in infant mortality rates from 1960 to 2003, 23 are in Sub-Saharan Africa (UNICEF, 2006). Countries like Zambia, Kenya and Botswana have even experienced an increase in their infant mortality in the last few years.

3.2.2 Northeastern Brazil

Northeastern (NE) Brazil (“Nordeste”) is the poorest region of Brazil. It consists of 9 states with a total population of 51 million in 2004 (IBGE, 2006). Life expectancy was
69 years of age and the IMR 34 in 2004 (MOH, 2006). All nine northeastern states are among the ten states with the lowest Human Development Index (HDI) in the country.

The region has over the centuries been considered as backward as compared to the more central parts in Brazil around Rio de Janeiro and São Paolo. From the 17th century and onwards sugar cultivation played an important role in the economy. Slaves were imported in large numbers to several of the states to work on the plantations. Where conditions were not optimal for sugar growth, cattle industry became a major source of income. In the interior of the territory a feudal system was established in which large land-owners wielded power over poor farm workers and tenants. An important element in the lives of people in the northeast was the drought which struck the region regularly and then led to famine and deaths due to starvation and epidemics (Barbosa, 1994).

As in the rest of Brazil, developments over the last 100 years in the northeast have been significant. Economic and health indicators have improved. An epidemiological transition is taking place in which non-communicable diseases increase their share of the burden of disease, especially in the cities (Barbosa, 1994). However, still many people suffer from infectious diseases including classic “tropical” diseases like leprosy, rabies, leptospirosis and Chaga’s disease. Diarrhoeal diseases also continue to be a health problem, particular in children.

A number of efforts have been made to reduce the effects of diarrhoeal diseases in Brazil. The Brazilian Ministry of Health (MOH) and prominent non-governmental organisations have been very active in promoting proper case management at home and
in health facilities since the mid-eighties. Strategies used have been national and regional mass-media campaigns on ORT and breastfeeding, training of government health workers and NGO-supported community health workers, and expanding health services through the construction of primary care facilities (Barros et al., 1989; Victora et al., 1996).

**The setting for the studies in 1989**

NE Brazil presented an interesting study site for the household and health facility surveys because at the end of the 1980s the region had been targeted for intense promotion of oral rehydration and correct management of diarrhoea cases. Sugar-salt solution based on mixing sugar and salt available in the household in water (soro caseiro) had been promoted by a large non-governmental organisation (NGO), Pastoral da Criança, through an extensive network of community health workers. UNICEF was also promoting the use of home-made rehydration solution. Simultaneously, the Ministry of Health was promoting the use of ORS packages. The packages were distributed through government health services. The MOH accepted the use of home-made sugar-salt solutions for prevention of dehydration but discouraged its use as a treatment for dehydration. The Ministry considered such solutions as potentially dangerous due to mixing errors, meaning that children would either not get adequately rehydrated or would run the risk of developing hypernatremia. The Pastoral da Criança on the contrary was of the opinion that encouraging people to use a treatment based on locally available and low-cost ingredients was empowering, giving people in local communities increased control of their own destiny. The Pastoral also claimed that the government health services functioned poorly, and that ORS packages often were out of stock. The standpoint of the Pastoral da Criança was supported by the Brazilian Pediatric Society that promoted the use of sugar-salt solutions through commercials over the national television network. Several different recipes were promoted for sugar-salt solution. All this meant that caretakers were exposed to conflicting messages on how to manage diarrhoea. It was in this situation that WHO proposed that a large-scale study be carried out to provide evidence of the acceptance and mixing skills of the different solutions as well as the availability of ORS in health services. The hope was that such data could help in solving the conflict between The MOH and the NGOs.

### 3.2.3 Ceará

Ceará is a state in the northeast of Brazil. The population of the state was 8.1 million in 2005. The economy in Ceará is still largely based on agriculture and fishing but a transition is gradually taking place towards an industrialised society with a growing urban middle class. 72% of the population now lives in settings which demographically are defined as urban. 27% of the people live in Fortaleza, the state capital.
Ceará is among the poorer states in Brazil. It falls on 20th place in the HDI ranking of the 27 states and territories in Brazil. 72% of the people are reported to have incomes below the officially defined poverty line.

During the past decade, progress has been made in many of the areas that are important in diarrhoea control. For instance, availability of piped water in households increased by around 17% 1991-2000 and in 2000 around 59% of households had tap water indoors. Availability of flush toilets in the household increased in the same period by around 5% and was estimated to be 32% in 2000 (SESA, 2002).

Data from the Secretariat of Health suggest that health indicators have improved significantly over the years. From 1997 to 2002, the infant mortality rate fell from 31 to 25 (MOH, 2006). As diarrhoeal deaths continue to contribute to the infant mortality rate (Terra de Souza et al., 1999) this change could also represent a reduction in diarrhoea-related deaths. Data from the routine reporting system suggest that diarrhoea mortality has decreased from 1985 to 2003 in Fortaleza but not in the rest of the state. This may in part reflect the uneven development of the state as Fortaleza has developed more than the rest of the state, not least in housing and provision of water and sanitation. Also, diarrhoea case management may be better in Fortaleza.
3.3 Data collection and data analysis

3.3.1 Household Survey in NE Brazil

In order to assess the impact on behaviour of interventions to improve diarrhoea case management a household survey was conducted in NE Brazil in 1989. The nine states in the northeast of Brazil were divided into four groups based on population size and geographical distribution. In each of the four states 80 clusters were randomly selected to allow for adequate representation of each of the states. In each cluster, 30 households were selected using standard methods for cluster household surveys in low- and middle-income settings (WHO, 1984; Bennett et al., 1991). 6,542 children under 5 years of age were surveyed.

In households, caretakers were interviewed by trained surveyors using a pre-tested questionnaire on diarrhoea incidence and management. In case a child had had diarrhoea in the 15 days preceding the interview, the caretaker was asked in more detail on action taken. An assessment of how well caretakers could prepare and administer oral rehydration was also done. Caretakers prepared these fluids in the presence of a surveyor. Samples of the prepared fluids were collected and later concentrations of sodium and osmolarity of the preparations were measured in a laboratory. Results were compared to recommendations made by WHO and the National Programme for Control of Diarrhoeal Diseases at the time of the survey.

The results from the survey were presented as frequencies with confidence intervals and related to on-going promotion of proper management of children with diarrhoea in the community.

3.3.2 Health Facility Survey in NE Brazil

In order to determine quality of diarrhoea case management in health facilities and to assess the impact of activities to improve that management, a health facility survey was done in NE Brazil. The nine states in NE Brazil were divided into four groups based on population size and geographical distribution. Through a stratified sampling technique 78 health centers and small hospitals were randomly selected. In each facility the infrastructure for diarrhoea management was ascertained, health workers interviewed for their knowledge on diarrhoea case management and case management in out-patient facilities observed by surveyors. Pre-tested forms were used for the assessments. Surveyors were nurses specifically trained for the work.

The results from the survey were analysed using standard statistical methods for distributions (frequencies with confidence intervals) and related to activities for promotion of proper diarrhoea case management in health services.

The two surveys (Paper I & Paper II) were conducted in the first half of 1989. The household and health facility surveys were carried out simultaneously with one surveyor in a field team conducting the health facility assessment while the other four did the household interviews.

I participated in the planning phase of the two studies in Pelotas, later took part in the training of the surveyors in Salvador, Bahia and then followed and supervised field
work in Ceará. I also took very active part in writing the two articles that report the results.

3.3.3 Assessment of Cross-sectional Household Surveys

A study was made of results from Demographic and Health Surveys (DHS) and surveys that had been carried out within WHO’s Programme for Control of Diarrhoeal Diseases (CDD). Within the DHS programme a module on management of diarrhoeal diseases had been included from early on in the programme. At the same time CDD had developed a manual for household surveys on diarrhoea case management (WHO, 1989a). As the DHS module had been made in close collaboration with CDD, countries could be identified in which information on the same variables on diarrhoea case management had been collected by separate surveys within a relatively limited time period and within the same sampling frame. This generated pairs of DHS and CDD surveys that could be compared to test the hypothesis that variation in survey results would be small as the underlying actual value would differ little between the surveys. Low variation would suggest good validity of the surveys.

24 countries were identified in which DHS surveys had been conducted from 1986 to 1989. With the help of a database of cross-sectional surveys on diarrhoeal diseases maintained by WHO in Geneva, nine CDD surveys were identified that fulfilled the criteria of having been conducted within a period of two years or less from the DHS survey in the same population. The variables ORS use rate, drug use rate, 24-hour diarrhoea prevalence rate and 2-week diarrhoea prevalence rate were compared in the surveys.

Chi square ($\chi^2$) test was used to test if there was a statistically significant difference between results from pairs of surveys from the same populations. The Spearman rank correlation was used to test if the two survey types yielded consistent results relative to ranking. For instance, a systematic over- or underestimation of a variable in either of the two survey types would generate the same ranking between the surveys even if paired results would differ. Using the comparison as a base, the validity and reliability of the surveys and possible sources of errors in data collection were analysed.

3.3.4 Trend Analysis of Diarrhoea Case Management in LMC

Trends for vital management indicators were analysed from DHS surveys to assess progress of diarrhoea case management in LMC. Variables studied were proportion of children given ORT, proportion of children that had received increased fluids, proportion of children that had not received increased amounts of fluids or ORT, and proportion of children for whom feeding had been continued during diarrhoea. Country trends for each of the indicators were assessed for all countries in which more than one DHS survey had been conducted from 1986 to 2003.

The overall trend for each variable was estimated using random coefficient regression. Findings were related to methodological and programmatic issues around health interventions in LMC.
3.3.5 Analysis of Diarrhoea Morbidity in Ceará

To explore progress in diarrhoea morbidity in a setting where diarrhoea still is common by international comparisons the state of Ceará in NE Brazil was used as study site.

Diarrhoea morbidity in 183 districts in the state was studied with information from three sources:

1. Sistema de Informação da Atenção Básica (SIAB) – a reporting system developed in 1998 to provide reports on community health parameters from community health workers in two out-reach programmes, PSF and PACS. The annual number of diarrhoea episodes per 1 000 children under two years old in households covered by the programmes was calculated and used as indicator of the incidence of childhood diarrhoea at community level.

2. Sistema de Monitoração de Doenças Diarréicas Agudas (MDDA) – a reporting system established in 1998 after a cholera outbreak in Brazil. All health facilities report their cases of diarrhoea through MDDA. With these data the annual health facility based morbidity rates per 1 000 children 0-4 were calculated.

3. Sistema de Informação Hospitalar (SIH) – a hospital-based reporting system through which all in-patient cases are reported. Incidence rates for admissions for gastro-intestinal infections were calculated as number of cases per 1 000 children 0-4 in the population.

Aggregated trends in diarrhoea morbidity and trends for each of the districts were assessed for the period 1998-2005 using a linear regression analysis.

To assess factors contributing to diarrhoea morbidity reductions, data on ten documented or assumed determinants of diarrhoea morbidity were collected. The determinants were HDI, income per capita, literacy rate, proportion of households with piped water indoors, proportion with flush toilet indoors, proportion of households connected to a garbage collection system, proportion of children below five years of age who were well-nourished, and proportion of children immunized against measles at one year of age. In addition, information on coverage of PSF and PACS was included in the analysis as studies have suggested that those programmes have had an impact on infant mortality (Macinko et al., 2006).

Data on background or underlying determinants were taken from publicly available databases from Instituto Brasileiro de Geografia e Estatística (IBGE, 2006), the federal Ministry of Health in Brasilia (MOH, 2006) and the Health Secretariat of Ceará (SESA, 2006).

Diarrhoea incidence was calculated for the period 2001-2004 for each of the three morbidity indicators. This was done to increase the time base of the outcome measurement as the impact of determinants is not immediate and likely to extend over longer periods than a year.

Linear correlations with p-values and simple linear regression were used to analyse the data. Sensitivity tests were performed under different assumptions about the quality of the data.
3.4 Ethical considerations

For the household survey and the health facility survey in NE Brazil ethical clearance was provided by the Ministry of Health in Brazil and by the Ethical Committee of the Universidade Federal de Pelotas, Brazil. Interviews were done by trained surveyors with informed consent from the participants.

The study of validity of household surveys and the study of global trends in diarrhoea case management were based on secondary data from already conducted surveys and did as such not require ethical clearance. The study on trends in diarrhoea morbidity and the association between morbidity and determinants used data from Ceará from official reporting systems and did not involve human participants. The study was cleared by the Secretariat of Health, Ceará and approved by the Ethical Committee of the School of Public Health (Escola de Saúde Pública do Ceará) in Fortaleza.

The major ethical consideration in the work was the issue of how to deal with acute cases of diarrhoea found during the household survey in NE Brazil. It was clear that surveyors would come across children with diarrhoea at the time of the visit to the household. To avoid ethical conflicts they had been advised to first complete the full interview including the mixing of fluids and then assess the child. If the child would show signs of dehydration that would require treatment by qualified health workers the family would be told to take the child to a near-by facility. Surveyors had varying skills in examining a diarrhoea case and they were therefore told to give priority to such referral when in doubt over a case.

Another ethical concern in both the household and the health facility survey was that caretakers and health workers interviewed and assessed may reveal incomplete or incorrect knowledge on diarrhoea management. It could be argued that in such instances the surveyors should convey information on correct management. The surveyors were mostly nurses so they did have skills on dealing with the disease but not necessarily up to the standard required to teach others. Nor were they trained for the survey to know the correct details of case management as the whole exercise was meant for data collection and not for health education or training. Mixing teaching and surveying could have affected data quality as caretakers could have influenced other caretakers’ knowledge during the survey. Still, if surveyors would come across grave mixing errors they were instructed to show the family how to prepare the solutions correctly before leaving the household.
4 KEY RESULTS

4.1 Case Management in Households (Paper I)

In the household survey in NE Brazil 982 (15%) of 6 524 children under 5 years of age surveyed had suffered from diarrhoea during 15 days preceding the interview. A total of 66% of the children were not taken for treatment, while government health services were used by 14%, private doctors by 1%, and traditional healers (rezadeiras) by 24%. ORT was given to 24% with details of preparations given in Table 4.

Table 4. Solutions given to children with diarrhoea in the household survey in NE Brazil 1989

<table>
<thead>
<tr>
<th>Solution given</th>
<th>% of children</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORS (packets from government services)</td>
<td>6.8</td>
</tr>
<tr>
<td>ORS bought in the market</td>
<td>4.3</td>
</tr>
<tr>
<td>Sugar-salt solutions (home-made from sugar and salt)</td>
<td>14.7</td>
</tr>
</tbody>
</table>

Although 95% of the caretakers knew about rehydration solutions, only 18% prepared them correctly, the most common error being the use of insufficient water. Of all the rehydration solutions used, 39% had a sodium concentration that was potentially dangerous (greater than 120 mmol/l). 8% had a sodium concentration that was very low leading to little or no rehydration effect.

Of solutions prepared using ORS packets, 38% had too high a sodium concentration, while 14% of the sugar-salt solutions prepared were too concentrated. The potentially most dangerous were the sugar-salt solutions prepared using non-standard recipes. More than half of those had an unacceptably high sodium concentration or osmolarity.

In summary, the study showed that ORT had been adopted but by relatively few families. Also, many caretakers could not prepare rehydration solutions correctly.

4.2 Case Management in Primary Care (Paper II)

The survey of primary care facilities in NE Brazil showed considerable variation in quality of diarrhoea management in children. 88% of the 78 randomly selected public primary care facilities in four states were health centers, while the rest were outpatient departments in hospitals. In 40% of the facilities, the number of monthly consultations of children was known, while 22% had information on the number of children attending for diarrhoea each month. 62% of facilities had a special ORT place for children as recommended by the national CDD Programme. Utensils for administration of ORT were available in only half of the facilities.

In 20% of the facilities the ORS packets were never or rarely available. In 32 of 65 facilities, the most recent shipment of ORS packets had arrived in the last month. Ten facilities had not received ORS for more than six months.
Seventy-five visits for childhood diarrhoea were observed in 42 health facilities. A physician was responsible for managing childhood diarrhoea in most facilities (86%). 90% of the patients were sent home, while the rest were treated under supervision. In 84% of cases ORT was prescribed, usually ORS packets. Antimicrobial drugs were prescribed in 21% of the cases. Other drugs like metochlopramide, caolin-pectin, aspirin and vitamins were prescribed in 41% of the cases. Health workers’ skills in history taking and examination were good with regard to asking about duration and frequency of diarrhoea and checking for skin elasticity and dryness of mucous membranes. Deficiencies were shown in asking about thirst and urine output and temperature, pulse and respiratory rate were rarely measured. In communication with caretakers, important information like recognizing signs of dehydration and recommendations on appropriate weaning foods was omitted by most health workers.

Overall, the study showed that case management based on ORT had been established in health services but also that deficiencies in case management and programme operations needed to be rectified.

4.3 Validation of Household Surveys (Paper III)

The comparison of DHS and CDD household surveys showed a variation in results that in around half of the cases was too large to be explained by a true variation in the variable studied. For ORT use rate, four out of 8 surveys showed results in line with the formulated hypothesis that differences would not be significant (Table 5). Three out of six surveys showed drug use rates in line with the hypothesis. Two out of four surveys showed 24-hour prevalence rates with little difference, while six out of nine surveys showed 2-week prevalence in line with the hypothesis. All other paired results showed differences that were statistically significant. The correlation between the two survey types was moderate with a Spearman correlation coefficient of 0.54.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of intersurvey comparison</th>
<th>Number of comparisons in which results were in line with hypothesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral rehydration solution use</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Drug use</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>24-hour prevalence</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Two-week prevalence</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

This study showed that household surveys may be influenced by systematic errors in data collection, compilation and possibly data analysis, a fact that needs to be considered when assessing results from household surveys and when defining their role in programme evaluation.
4.4 Diarrhoea Case Management in LMC (Paper IV)

The study on diarrhoea case management in LMC showed that progress had been slower than desired from a disease control point of view. A total of 107 surveys in 40 countries fulfilled the criteria for inclusion in the study. Data on the indicator “Proportion of children given ORT” were available from all countries. The overall trend over time was estimated to an annual increase of 0.39% (p=0.089) (Figure 4). Twenty-three (58%) of the countries showed a positive development of the indicator. Seventeen (43%) had a larger increase than the average trend.

Data on the indicator “Increased Fluids” from more than one survey was available from 38 countries. The overall trend over time was estimated to an annual increase of 1.02% (p<0.01). Twenty-six (68%) of the countries showed a positive development of the indicator. Twenty countries (53%) had a larger increase than the average trend.

Sequential data on the indicator “Percentage of children given no ORT or Increased Fluids” (called “no fluid” rate) was available from 37 countries. The overall trend over time was estimated to an annual decrease of 0.64% (p=0.041) (Figure 5). Twenty-one (57%) of the countries showed a reduction of the indicator and 16 (43%) an increase. Eighteen (49%) had a lower decrease than the average trend.

Questions on amounts of food given to the child during diarrhoea were included in 38 out of the surveys. However, only 14 countries showed comparable and plausible survey data. The overall trend over time was estimated to an annual decrease of 0.58% (p=0.42). Five countries (38%) showed positive development of the indicator and nine (62%) negative. Seven (54%) had a larger positive development or decreased less rapidly than the average trend.

The study did not provide evidence that diarrhoea management in low- and middle-income countries had progressed during 1986–2003 according to targets and intentions. Essentially, use rates developed much slower than expected and achievements were far below the targets set by WHO and UNICEF at the beginning of the 1990s (WHO, 1994).
Figure 5. Estimated mean trend in children given no ORT or increased fluid intake as documented in 92 DHS surveys in 36 low- and middle-income countries.

In a separate analysis of DHS data from 1999-2003 it was found that the overall ORT use rate in the surveyed child population for that period was 40%, the ‘increased fluid’ rate was 34% and the ‘no fluid’ rate was 44%. If these numbers are representative of low- and middle-income countries, then 307 million children aged under 5 years did not get ORT, 356 million did not get increased amounts of fluids and 227 million children with diarrhoea got neither ORT nor increased fluids during diarrhoea at the beginning of the 21st century.

4.5 Diarrhoea morbidity in Ceará (Paper V)

In the study from Ceará three indicators of diarrhoea morbidity showed a down-ward trend from 1998 to 2005. Only the trend measuring hospitalisations of children for diarrhoea was statistically significant (p<0.001). Out of 183 districts studied, 71.3% showed a down-ward trend for the community diarrhoea incidence indicator, 65.6% a down-ward trend for the health services diarrhoea incidence and 65.6% a down-ward trend for diarrhoea hospitalisation incidence.

The associations between determinants and the three indicators of diarrhoea morbidity are presented in Table 6 in which correlation coefficients and regressions with p-values are given.

The associations between income per capita and the community diarrhoea incidence, and between adult literacy and the community diarrhoea incidence, were statistically significant. No other associations were significant, but diarrhoea was reported less frequently from households with higher income and higher literacy. Most of the other determinants showed a weak correlation with the diarrhoea incidence indicators.
Table 6. Correlation coefficient, regression coefficient with p-values for determinants of diarrhoea and three indicators of diarrhoea incidence.

<table>
<thead>
<tr>
<th>Determinants</th>
<th>Community Incidence</th>
<th>Health service Incidence</th>
<th>Hospitalisation incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation coefficient</td>
<td>Regression coefficient (p-value)</td>
<td>Correlation coefficient</td>
</tr>
<tr>
<td>% of households with piped water, 2000</td>
<td>0.04</td>
<td>0.21 (0.57)</td>
<td>0.15</td>
</tr>
<tr>
<td>% of households with flush toilets, 2000</td>
<td>0.01</td>
<td>0.04 (0.91)</td>
<td>0.11</td>
</tr>
<tr>
<td>% of households attached to garbage disposal services, 2000</td>
<td>-0.10</td>
<td>-0.52 (0.19)</td>
<td>0.08</td>
</tr>
<tr>
<td>Human Development Index, 2000</td>
<td>-0.12</td>
<td>-277.64 (0.10)</td>
<td>0.04</td>
</tr>
<tr>
<td>Income per capita, 2001</td>
<td>-0.16</td>
<td>-0.62 (0.03)*</td>
<td>0.08</td>
</tr>
<tr>
<td>% of children immunized against measles at 12 months of age, 2000</td>
<td>0.10</td>
<td>0.57 (0.18)</td>
<td>0.02</td>
</tr>
<tr>
<td>% of children with normal nutrition status, 2000</td>
<td>-0.12</td>
<td>-14.51 (0.15)</td>
<td>0.11</td>
</tr>
<tr>
<td>% of adults literate, 2000</td>
<td>-0.26</td>
<td>-4.05 (0.00)**</td>
<td>0.05</td>
</tr>
</tbody>
</table>

* signifies p<0.05. ** signifies p<0.005
5 DISCUSSION

5.1 Main Findings

Diarrhoeal diseases constitute a major disease burden on children in low- and middle-income countries (LMC), with an estimated 2 million 0-4 years old dying annually due to diarrhoea. Dehydration is the main cause of death. ORT is the primary tool to reduce case-fatality from diarrhoea. Proper nutrition is also essential for survival. Socioeconomic development and broad public health interventions are needed to reduce incidence. In this thesis I have conducted studies of diarrhoea over a period of almost 20 years, providing a valuable perspective on major public health interventions to reduce diarrhoea morbidity and mortality. The thesis provides evidence that diarrhoea case management has improved in LMC over the period but not as much as expected.

In the study from NE Brazil in 1989 presented in Paper I it was found, that 24% of children with diarrhoea received ORT after intense promotion of such therapy. 95% of the caretakers knew about rehydration solutions, but only 18% prepared them correctly. In primary care services ORT appeared to be widely accepted in the same region, but still quite a few facilities lacked the proper infrastructure for proper implementation of ORT and health workers’s skills in case management needed to be improved (Paper II). Those two studies carried early evidence that ORT was not easily adopted and applied properly. More recently, findings in Paper IV indicate that diarrhoea management in LMC has not progressed during 1986–2003 according to targets and intentions. Essentially, use rates developed much slower than expected and achievements were far below the targets set by WHO and UNICEF at the beginning of the 1990s (WHO, 1994). From the household survey data, it was estimated that 307 million children did not get ORT and 356 million did not get more to drink during diarrhoea at the beginning of the 21st century.

It is possible that more attention to the problems identified in the Brazil studies could have contributed to a better acceptance of ORT in low- and middle-income countries. Mixing errors as identified in Paper I will make the oral rehydration solution less effective, creating a risk that disappointment with the solution will discourage parents to use ORT again. More attention to the obstacles to proper mixing and utilization could possibly have prevented such reactions. From the results in Paper IV it can be concluded that there is a need to look in more detail how case management of diarrhoea in children is perceived and practiced by caretakers. Such research can further enhance the knowledge on how use of ORT and other positive case management measures can increase in the community.

Performance in health services is likely to contribute significantly to dissemination and overall acceptance of preventive measures and correct case management. The study of health facilities and health workers in NE Brazil in 1989 showed problems that needed to be addressed to improve case management. For instance, one fifth of health facilities did not have rehydration packets in stock. Given the results in Paper IV, the role of health services for prevention of diarrhoea and proper use and management of ORT in the community should be further studied, preferably with intervention studies covering both public and private actors.
In the study on household survey results from comparable surveys (Paper III), around half of the survey pairs showed a statistically significant variation, contrary to the hypothesis of no difference. This pointed to the possibility of systematic errors in data collection in household surveys and possible sources of errors were discussed in the paper. The study showed the need for more in-depth studies of how to improve methods for data collection in households.

The recent study in Ceará, Brazil (Paper V) provided some evidence, though weak, that diarrhoea morbidity went down slightly 1998-2005. The decline was strongest for diarrhoea admissions (p<0.001) suggesting an improved overall case-fatality rate from diarrhoea. Few determinants of morbidity could be associated with any of the three indicators of diarrhoea morbidity in a comparison of 183 districts in the state. The study confirmed the pattern seen in LMC that diarrhoea morbidity has not gone down much in the past 20 years. The reasons for this should be further explored.

5.2 Methodological Considerations

The following section discusses the three main instruments used for data collection and data analysis in this thesis: household surveys, health facility surveys and routine reporting in health services.

5.2.1 Household Surveys

The household survey method is an essential tool in public health research and evaluation (Bowling, 2005). The general strength of the household survey method is that it provides data that are representative of the community as a whole. It allows for collection of information that cannot be easily collected through routine reporting systems, such as knowledge, attitudes and practices of people. It is the best way to estimate incidence and prevalence of common conditions that are not routinely brought to health services. Further, management of cases with diarrhoea can be investigated irrespective of whether or not they have been taken to health services.

A short-coming of household surveys is that the information collected is based on stated practices rather than actual. Reasons for discrepancy between the two may be that people recall actual behaviour inaccurately (Kroeger, 1983; Fabricant & Harpham, 1993), that people report desired behaviour rather than actual (Ross & Vaughan, 1986), that they perceive or understand concepts differently than intended by the surveyors (Larsson & Mitra, 1992) or that they do not see reporting of actual practices as important and therefore may be careless in responding.

Recall errors

Recall problems can affect diarrhoea morbidity reported through household surveys. It has been shown that diarrhoea illness episodes tend to be overlooked the further back from the time of interview they occur and the less severe they are (Alam et al., 1989). However, the short recall period of two weeks for diarrhoea illness in household surveys is used to reduce this source of error. Stanton et al. (1987) compared two-week diarrhoea diaries maintained by household members with those histories given in
response to a two-week health recall interview and found little difference between the two. This would strengthen the argument that diarrhoea household surveys using two-week recall provide relatively accurate estimates of diarrhoea prevalence. Still, there are reports of under-reporting diarrhoea in such surveys (Goldman et al., 1998). Boerma et al. (1991) found in a review of data from 19 DHS surveys that reporting errors varied considerably between countries. They also found that there was under-reporting of diarrhoea if the recall period was longer than 2-3 days, whereas there was possibly over-reporting of very recent or current diarrhoea in the surveys.

If there is a tendency to under-report diarrhoea episodes in household interviews then prevalence rates as documented through surveys would evidently be underestimates. Still, household surveys in Ceará showed a much higher incidence rate (Correia et al., 2003) than reported through the health services as described in Paper V. Similarly, diarrhoea prevalence rates reported in DHS surveys are relatively high. These data call for more research on how well household interviews can measure diarrhoea prevalence and incidence. Such research could for instance be done by comparing reports from daily visits by community health workers with information from two-week recall interviews. So far there are very few studies of this kind (Stanton et al., 1987; Goldman et al., 1998). The research is essential as household surveys are crucial in determining progress in diarrhoea morbidity as well as in evaluation of interventions aimed at reducing diarrhoea morbidity.

Recall problems with regard to treatment could relate to being oblivious about treatment given in the early stages of an episode that is over at the time of the interview. Treatments that have been actively purchased or received from health services are more likely to be remembered than those taken from an available stock in the household or given by neighbours. The more active the treatment, the more likely it is to be remembered. Proper application of oral rehydration is therefore less likely to be under-reported because of poor recall as it is a time-consuming activity. Utilization of drugs that are regularly used are more likely to be under-reported.

**Incorrect reporting**

Incorrect reporting could be due to the respondent seeing some actual or potential benefit from reporting an illness or a treatment. This would probably not be present in the case of diarrhoea as there is no reward linked to reporting such an episode in household surveys. However, a study in England of a diarrhoea outbreak that got much attention in media showed that diarrhoea was significantly over-reported in a population survey that was conducted during the outbreak (Hunter & Syed, 2001).

Inaccurate response could also be due to questions being formulated in a leading way or presented so that the respondent gets the impression that a particular answer is preferable (Bowling, 2005). This is less likely to have affected the results in the studies included in this thesis. In the DHS surveys analysed in Paper III and Paper IV, questions on diarrhoea have been part of more extensive interviews and have not stood out as particular. Also, the questions in the standard DHS and Brazil surveys are open-ended and formulated to be neutral.
The psychology and thoughts in the community around household surveys and the information they collect needs to be further explored in order to determine if under- or over-reporting occurs. In a work from Zaire (Congo), Haggerty et al. (1994) found that people would over-report episodes as having started or terminated on the day of the interview, illustrating that there are various ways in which data get influenced by factors related to the interview situation. In a study of self-reported diarrhoea in the United States it was found that people tended to under-report diarrhoea as compared to what would be considered diarrhoea by physicians (Talley et al., 1994). All this point to the need for better understanding of the validity of household survey data.

With regard to case management practices incorrect reporting due to social pressure to report certain behaviour cannot be excluded. Governments and NGOs have put significant efforts into promoting certain types of treatment, in particular ORT. This could have made caretakers over-report use of ORT. However, ORT use rates in the surveys analysed in the thesis have generally been lower than expected. Hence, potential over-reporting should not have affected the important conclusion from the thesis that ORT use is far from satisfactory in LMC.

The likelihood that people will report illnesses in surveys inaccurately will also depend on the degree to which the disease is considered shameful, a disease that people want to hide. It is less likely that such sentiments have affected results in diarrhoea surveys in LMC where diarrhoea is such a common disease. There is little evidence from anthropological research on diarrhoea that this would be important (Stapleton, 1989; Choprapawon et al., 1991; Ellis et al., 2007). Diarrhoea in children is mostly considered an every day event that is part of normal life, at least in lower socio-economic groups.

**Problems of understanding and communication**

A factor that may affect reported diarrhoea is the understanding of the concept or term used in the interview. Wright et al. (2006) showed that using different definitions of diarrhoea could generate estimates of annual diarrhoea morbidity that varied from 38% to 137% as compared to the standard two-week recall period. I was engaged in a survey in which different translations of the word “diarrhoea” into the vernacular Tagalog during a field test of a questionnaire in the Philippines lead to wide differences in reported incidence. One translation meant “soft stools” while the other actually meant the illness diarrhoea – the word people commonly used for what was felt to be a genuine case of an illness (Forsberg, 1994).

In the DHS surveys significant work is put into translating questionnaires into local languages. Finding the correct term for diarrhoea is of high priority. However, there are still countries in which this may be a challenge as there may not be one particular word comprising all the types of diarrhoea that would be covered by the standard scientific definition of diarrhoea (Mushtaque et al., 1991; Kalthenthaler & Drasar, 1996). The different way people translate and perceive diarrhoea is a potential source of error in cross-country comparisons of diarrhoea prevalence and incidence.

**Survey quality improvements and training**

A possible source of error in trend analysis based on information from household surveys is that changes in surveyor training and skills over time may affect precision
and validity of data. For instance, if skills on how to train surveyors improve over time, there may be a systematic change in reported rates when surveyors become better at getting valid answers from respondents. This must be considered a risk in the study on global developments of diarrhoea case management presented in Paper IV. If rates were over-reported in early stages the lack of progress may reflect improved quality of the data rather than actual changes or lack of changes. The thesis contains an example: in early DHS surveys continued feeding rates were reported to be implausible 100% in several instances. Later, similar rates could not be repeated in subsequent surveys, probably because the technique to ask on feeding practices during diarrhoea had improved.

5.2.2 Health Facility Surveys

The research instrument used in the study of health facilities from Brazil is based on the concepts structure, process and outcome (Donabedian, 2003). In this case, the outcome is only assessed indirectly through the structure and process observations. Both the structure and process methods are linked to possible errors. In particular, the risk of a “Hawthorne” effect must be considered (Campbell et al., 1995; Holden, 2001; Mangione-Smith et al., 2002). This means that persons observed tend to perform differently, and usually better, when they are observed. With regard to structure this may result in improvements of facilities before the arrival of the surveyor. For instance, premises may be cleaned, equipment and drugs bought or brought in from outside and staff may be more available than usual. The process of receiving, examining and treating patients may be done better than usual in the presence of a surveyor. In the case of the study in Brazil, both these factors may have been less important as health workers in the premises did not see a direct link between the research assistants and the supervisors in the public health care system. Even if the study did report better structure and behaviour than the actual, it did not prevent the documentation of a number of problems in the health facilities, problems that required urgent attention.

The technique used in Paper II became the standard for CDD health facility surveys subsequent to the study in NE Brazil (Forsberg et al., 1992). The same technique is now applied in the IMCI health facility surveys (WHO, 2003; Duke et al., 2006) as well as in research on malaria (Eriksen et al., 2007). Overall the method has been deemed to be sufficiently valid, relevant and useful to be applied at a larger scale. From a programmatic point of view its usefulness is supported by the experience from Brazil, documented in Paper II. In a review published by the Health Metrics Network it was concluded that “facility surveys are a missing component in national Health Information Systems and can provide essential data for monitoring health-system resources, service norms and quality and for programme-evaluation purposes” (Health Metrics Network, 2006b). Still, few systematic studies of health facility surveys as method have been done and the knowledge on validity and precision of this methodology should be expanded.
5.2.3 Routine Reporting

The study of diarrhoea morbidity and its determinants in Paper V relies on data collected through routine reporting in the health system. In spite of the significant importance of routine reporting systems, few studies have actually analysed the quality and methodological issues of routine reporting in LMC (Lippeveld, 2001; Abou-Zhar et al., 2005; Merson et al., 2005). The precondition for success are also little known and methods for quality assessment and assurance are not well established. Recent work in the Health Metrics Network seeks to address these issues (Health Metrics Network, 2006a). Evident indicators of quality are reporting rates, regularity of reporting, completion of forms and validity of results. However, we know little about how to assess each of these indicators in relation to desired goals of routine reporting systems.

In the study from Ceará it was found that reporting was weak at the onset of the MDDA diarrhoea reporting system but that it quickly improved and reached a high degree of participation. Overall, case reporting was regular and yielded plausible results. The data reported from districts appeared to have good validity. More disturbing was the poor correlation with underlying or proximal determinants. Few of the determinants showed a positive association with decreasing diarrhoea incidence. Many of the determinants were measured through household surveys. Hence, the discussion above on possible sources of errors in such surveys is relevant. An argument for high validity of the data on most determinants is however that the data come from a national census carried out in 2000 by the Brazilian Institute of Geography and Statistics (IBGE, 2006). The Brazilian censuses use standard protocols and they are conducted in a meticulous manner by well trained staff. Also, some of the variables like availability of water and sanitation should have high validity. Even so, one must be open to the possibility of varying accuracy of the wide range of data used in the study presented in Paper V.

5.3 Discussion of Main Findings

5.3.1 Problems in Adopting and Practicing ORT

The two first studies (Paper I & Paper II) show that significant efforts in Brazil to promote diarrhoea case management had an impact in NE Brazil in the eighties. At the same time, the thesis also documents that diarrhoea case management is associated with several problems at household and health facility levels. In a review of data on case management from household surveys in a number of low- and middle-income countries in Paper IV it was found that use of ORT levelled off in the 1990s in particular. A similar pattern was seen in Ceará where ORT practices have remained relatively unchanged since the early stages of programme implementation (Correia et al., 2003) when the household survey in Paper I was carried out. Progress in diarrhoea case management appears to have been limited over the last decade.

The household survey in NE Brazil reported in Paper I showed that the majority of caretakers dealt with their children’s diarrhoea themselves. This shows that communication on correct home management to caretakers is vital. Still, it was found in the study that knowledge is not enough. Though almost all caretakers knew about rehydration, only a quarter actually gave it to their children. In the assessment of quality
of rehydration solutions prepared by caretakers it was seen that less than half of solutions were prepared correctly. Promotion of at least three different recipes from different actors was judged to have contributed to this problem. It was concluded from the study that interventions for the use of ORT should have a uniform message and promote only one recipe for home preparation of rehydration mixtures.

It was shown already in 1979 that caretakers could have significant problems in mixing oral rehydration fluids from ingredients available in households (Cutting et al., 1979). The same study showed much better results when caretakers were given a packet of powder to mix in water. The findings were one reason why WHO decided to promote the use of ORS packets rather than home-mixed solutions based on sugar and salt. Hutchins et al. (1980) found that most parents could use a packet with reasonable accuracy although there were still wide extremes of errors in the preparations. De Zoysa et al. (1984) studied concentration of home-mixed sugar-salt solutions in Zimbabwe. Only 26% of caretakers in their sample prepared a solution with sucrose and sodium concentrations within a safe and effective range. In another study from Zimbabwe, it was found that the majority of mothers were competent in preparing the solution, but the mean sodium concentration of the solutions prepared were significantly lower than the recommended standard safe range of 50-80 mmol/liter (Nyatoti et al., 1993).

Interestingly, a study in Egypt showed, that the mean ORS sodium concentration for a group supplied with a standard cup (200 ml) was significantly lower (98 mmol/L) than the ORS sodium concentration (123 mmol/L) of a group that used ordinary home containers (El-Mougi et al., 1984). Both groups were given a package of ORS to use in preparation of an oral rehydration fluid. In fact, the study suggested that preparation of ORS from a package with a concentration of 90 mmol/l was not that easily done and that it could potentially expose children to high concentrations of sodium.

These studies pointed to the difficulties in preparing oral rehydration fluids at household level. The study in Brazil confirmed this at a larger scale. In spite of the compelling evidence, little attention was paid and is still paid to these findings. Few studies in the last 15 years have really assessed the quality of oral rehydration at household level and there is little knowledge on how well ORT is practiced in the community. There is clearly a need for more research on this. Poor ORT fluids may lead to failed treatments putting the child at risk of dying from dehydration. It can also expose children to the risk of hypernatremia, even if this risk should be lower with the new WHO formula than before. Poor treatment results can discourage the caretakers from further use of ORT.

Both the study in NE Brazil (Paper I) and the study of LMC (Paper IV) showed lower use of ORT than desired. Some of the possible reasons for unsatisfactory adoption of oral rehydration and correct management of diarrhoea are discussed in the following.

**Competing priorities in households**

One reason why progress on diarrhoea control in LMC has been far from satisfactory may be that efforts to change practices in households and in health services have not been sufficient. Another reason could be that those efforts have not been effective. Adequate home-based care may not have been sufficiently emphasized to convince caregivers to give it priority. In resource-scarce settings, caregivers’ attention is split
between multiple obligations that are essential to the survival of the family. Decision-making during illness is influenced by many factors in poor households (Pokhrel & Sauerborn, 2004). Knowledge on oral rehydration may be adequate but may not be applied in an environment of competing priorities. This explanation finds some support in earlier studies of DHS data where it has been consistently found that knowledge on ORS is considerably greater than actual use of the fluid (Ryland, 1998). The same was recently also reported from a study in Malawi (Ellis et al., 2007). It is possible that families need to appreciate better that proper management of a child with diarrhoea demands considerable time and attendance. Programme managers should appreciate the opportunity cost to households of case management (Philipson & Posner, 1993). More emphasis should be given to ORT as a remedy that maintains the strength of the child during illness and as a potentially life-saving measure well worth the effort it requires. There is a challenge in making families spend time on ORT for a condition that is so common that it is not seen by most caretakers as a potential threat to life.

Community concepts and beliefs
People in general in the community may have ways of looking upon diarrhoea that differ from those of medical professionals or public health managers. It has been documented from a number of countries that diarrhoea is not one entity or concept among common people. Its perceived causes and the action taken may differ from episode to episode and from one type of diarrhoea to another. In Thailand, Choprapawon et al. (1991) found that people used another term for diarrhoea in everyday life than the one the Ministry of Health was using in its campaigns for promotion of ORT. The term the Ministry used defined a more serious type of diarrhoea than the local term used for diarrhoea in everyday life. ORT was only seen as needed for some types of diarrhoea among common people while the Ministry sought to promote it for diarrhoea in general. In Nepal, Stapleton (1989) found that “hot” or “cold” factors as cause of different types of diarrhoea were considered important for people’s choice of treatment. ORS mixed in cold water, as recommended by the national programme, would therefore not be acceptable as treatment for some diarrhoea conditions.

The importance of considering local beliefs and traditions when designing health interventions, including diarrhoeal diseases control, has been underlined and discussed by several researchers (Pelto, 1987; Bentley et al., 1988; Stanton et al., 1992; Kauchali et al., 2004). As pointed out by Kauchali et al., conceptual mismatches between local beliefs and concepts and medical terms and classifications used in disease control programmes carry the potential to hamper health promotion, predispose to delayed and poor care and may lead to selection bias, under- and misreporting and poor compliance in research.

Competing treatments in the market
Another circumstance that may have hampered the adoption of ORT is that competing treatments may divert attention from ORT. For instance, ineffective drugs are promoted and sold to families as treatment of diarrhoea (Muhuri et al. 1996). In a review of DHS data from 1996–2002 it was found that pills, syrups, injections, or intravenous fluids...
were given to 50% or more of children with diarrhoea in 36 out of 50 surveys conducted during the study period (Stallings, 2004). Evidently, use of such remedies may compete with ORT and feeding. Marketing or incorrect advice is important in this. The often documented wish of caretakers to “stop the diarrhoea” (Ellis et al., 2007) contributes to the demand for drugs. The fact that ORT does not reduce the frequency or volume of diarrhoea stools has been a matter of concern to WHO and the diarrhoea research community for many years (WHO, 1999a). It has been one of the reasons behind the search for a “super-ORS” which could not only increase absorption of fluids from the intestine but also reduce the severity and duration of diarrhoea by binding water so that stools become more solid and the intestinal passage of excreta is slowed down (Elliott et al., 1990; Gore et al., 1992; Gore et al., 1996). This research has been focused on developing cereal-based rehydration solutions. So far, it has been met with limited success (Fontaine et al., 2000). Hopefully, the new ORS formula should be more effective and popular among the public.

A great number of diarrhoea cases are taken directly to drug vendors and pharmacies in developing countries (Stallings, 2004). If they would be advised on proper case management there it could make a contribution to a reduction of case-fatality. However, studies since 1986 to 2005 have consistently shown that drug vendors tend to over-prescribe drugs and under-prescribe ORT (Tomson & Sterky, 1986; Bojalil & Calva, 1994; Haak & Claeson, 1996; Chuc & Tomson, 1999; Larsson et al., 2000; Stenson et al., 2001; Syhakhang et al., 2001; Das et al., 2005). The discrepancy between knowledge and actual behaviour is particularly apparent and disturbing in this group (Chalker et al., 2000; Chuc et al., 2001). Still, studies have shown that drug vendors’ behaviour can be influenced through training and information (Ross-Degnan et al., 1996; Laing et al., 2001)

Not reaching the poor

Another possible reason for the inadequate coverage of proper case management is that programme messages may not have reached all target groups and in particular those with the highest risk of mortality (Ibrahim et al., 1994; Hong et al., 2003). In Stalling’s study of DHS it was found that mothers with a higher level of education were more likely to adopt messages on diarrhoea management. Caregivers that were in contact with health services were more likely to use rehydration therapy than others (Stallings, 2004). Generally, use of services is more common in higher income groups (Wagstaff et al., 2004). It has also been documented that health workers in public services at times are rude and non-communicative with clients (Murira et al., 2003). In Vietnam, it was found that such behaviour was particularly common towards the poorest, a fact that may have contributed to their low utilization of health services (Hong et al., 2003).

It has been proposed in the last few years that child survival programmes must become more targeted towards poor and vulnerable groups to increase their effectiveness further (Claeson et al., 2003; Schellenberg et al., 2003; Victora et al., 2003). More intensified research on how to reach households that do not yet apply correct case management when their children get diarrhoea is of high priority to further reduce mortality from diarrhoeal diseases in children (Victora et al., 2003). Recent research from Bangladesh has shown that specific interventions to reach the poor can work (Ahmed et al., 2006).
Without reaching the most vulnerable and destitute, the Millennium Development Goals (MDG) cannot be achieved.

**Case management in health services**
The lack of progress in adopting ORT at community level could possibly have been countered by an improvement of diarrhoea case management in hospitals. Such improvements have taken place (Hatch et al., 1990; WER, 1988) but at the same time results from health facility surveys or special studies have suggested that this progress has not been universal or consistent in health facilities (WHO, 1994). The study of health facilities in NE Brazil in Paper II pointed to shortcomings in diarrhoea management in primary health services. In another study from the same region it was found that the procedure used to rehydrate patients with ORS was correct in only 6% of the cases. Of those patients with bloody stools, only 24% were treated appropriately with antibiotics (Ribeiro Junior & Drasbek, 1995). Again, these findings came from an environment in which diarrhoea case management had been much promoted. These findings are a matter of concern and calls for further research on how to improve diarrhoea case management in health services and among health professionals.

**Integrated Management of Childhood Illness (IMCI)**
A reason why diarrhoea case management has not progressed as desired may be that when IMCI was established in the mid-90s it took attention away from diarrhoea. Leading organisations like WHO and UNICEF could not put emphasis on the previously supported activities for control of each of the diseases covered by the IMCI approach. As a result, diarrhoeal diseases control programmes may have received lower priority at national level in many countries (Gwatkin, 2006). The policy of WHO was to recommend countries to introduce IMCI in a phased manner starting with a few districts to try out the programme before it was launched nationwide (WHO, 1999b). As each phase takes several years, the outcome so far is that few countries have national IMCI programmes with more than 75% of districts covered by the programme (WHO, 2004a). This may have left a gap in promotion and education on proper diarrhoea case management.

Intervention studies suggest that IMCI is an effective way of reducing child mortality from the target diseases (Armstrong Schellenberg et al., 2004; El Arifeen et al., 2004). The studies were however done under circumstances where IMCI was piloted with significant attention and resources allocated to the programme. It has also been documented that IMCI targeted better off districts in the countries where it was promoted (Victora et al., 2006). A large-scale multi-country evaluation of IMCI (Bryce et al., 2004) has pointed to several challenges in implementing the model. Four of five countries evaluated in more detail had difficulties in expanding the strategy at national level while maintaining adequate intervention quality. Technical guidelines on delivering interventions at family and community levels were slow to appear, and in their absence countries stalled in their efforts to increase population coverage with essential interventions related to care-seeking, nutrition, and correct care of the sick child at home (Bryce et al, 2005b). Further, recent research from Brazil could not document an association between IMCI health worker training and infant mortality rate.
 reductions (Amaral et al., 2005). These findings are a matter of concern. It still remains to be seen if the IMCI approach can be effective in an ordinary setting where health workers work routinely with management of sick children. It also needs to be seen how well it covers each illness.

**Inadequate resources for child health**

A particular challenge in scaling up IMCI and other important child health interventions are the costs involved even though it has been shown from Tanzania that IMCI does not cost more to implement than ordinary health services (Adam et al., 2005). Still, special efforts are needed to reach all with this and other interventions. A recent study by Stenberg et al. (2007) shows that LMC have a substantial investment gap to bridge in order to reach the fourth MDG on child health. The study predicts that an additional US$ 52.4 billion will be required to that end for the period 2006-2015 in 75 LMC, representing an increase in total per-capita health expenditure from US$ 0.47 in 2006 to US$ 1.46 in 2015. It is possible that the main reason for unsatisfactory adoption of diarrhoea case management in LMC is that resources set aside for diarrhoeal disease control and child health programmes and interventions have been insufficient up to now (Kallander, 2007).

5.3.2 Household Surveys in Programme Evaluation

The study comparing household survey results presented in Paper III showed a variation in diarrhoea prevalence and treatment rates between the surveys that could not be explained by actual changes in the indicators assessed. The article identified factors described above as possible explanations for the finding. The article pointed to the limitations of household surveys. Household surveys provide useful information on health and related matters supplementary to data collected through routine reporting or sentinel surveillance. Household surveys also have a role in programme evaluation when the differences to be measured are of the magnitude that they can actually be measured with the survey method and standard statistical analysis of the results (Bowling, 2005). Household surveys may however be less useful for regular programme evaluation when the expected impact from an intervention is limited as compared to the baseline value. To illustrate, surveys will need larger samples to measure a statistically significant change of 10% from a baseline of 80% as compared to a baseline of 10%. This fact is at times not given sufficient attention when household surveys are included as routine evaluation tools in programme implementation. The sample of the survey will depend on the baseline and the change that the programme has set as a target (WHO, 1984). The sample size has immediate implications for the cost of the survey. The principal cost of an impact or programme evaluation is the cost of data collection (Savedoff et al., 2006). Household surveys in programme or impact evaluation should be carefully assessed and their potential benefits weighed against their cost. The assessment should include an analysis of what other means of verifying the impact from a programme or an intervention that could be available (Kirkwood et al., 1997; Bryce & Victora, 2005). Some examples are qualitative studies (Nichter, 1991), rapid assessments (Bentley et al., 1988) and health facility surveys (Forsberg et al., 1992). Decision makers should be made aware that evaluation costs increase rapidly with
complexity and the need for detailed and precise answers. A compromise must therefore often be reached between costs, data quality and precision (Habicht et al., 1999).

5.3.3 Limited Reduction in Diarrhoea Morbidity

In this thesis, I have analysed recent data on diarrhoea morbidity in Ceará from health services (Paper V). Results suggest that diarrhoea morbidity as reflected through attendance at health facilities is decreasing. The findings are however not conclusive on diarrhoea morbidity in the community. Earlier studies on diarrhoea morbidity in LMC have not documented a significant decline in morbidity rates in the past 10-15 years (Kosek et al., 2003). In Ceará, household surveys have shown a similar pattern (Correia et al., 2003).

It remains an enigma why diarrhoea incidence has not gone down significantly in low- and middle-income countries that have undergone considerable development in factors vital to diarrhoea disease control, like provision of water and sanitation (WHO, 1997; WHO, 2000).

The study from Ceará (Paper V) could not document a clear link between diarrhoea incidence rates and differences in coverage of morbidity determinants at municipality levels. Specific studies of interventions to improve such factors at household level have shown that they can reduce diarrhoea incidence (Cairncross & Valdmanis, 2006; Clasen et al., 2006). The finding from Ceará fits into a model for disease development in which it is the collective and comprehensive effects of development on many factors simultaneously that influences the burden of disease on a population (Berrebi & Silber, 1981; Caldwell, 1993; Chung & Muntaner, 2006). It may be possible to show impact on diarrhoea morbidity from each factor separately when it advances more than others as is the case in intervention studies, but its effect in comprehensive development may be more difficult to separate out.

5.3.4 Mortality, Morbidity and Case-fatality Discrepancies

It appears that diarrhoea mortality has gone down in developing countries while diarrhoea morbidity has remained largely unchanged. If so, then the mortality reduction must be due to a falling case-fatality rate. A decrease in case-fatality could depend on diarrhoea episodes becoming less severe, or on improved diarrhoea case management.

Factors that contribute to a reduction of severity of diarrhoea are factors that strengthen the ability of the individual to resist the infection or factors that reduce the risk of getting infected with aggressive microbes that are more virulent than others. In the first instance, the factors that have been shown to be most prominent in enhancing the immunological defence against diarrhoea in children are nutrition (Barros et al., 1995; Hanson, 1999) and measles immunization (Feachem & Koblinsky, 1983). The coverage of measles immunization has gone up over the past 15 years (WHO, 2006a; Elliman & Bedford, 2007) so this should have a positive impact on case-fatality. With regard to malnutrition the proportion of children suffering from severe malnutrition appears to
have gone down (even though the progress is far from satisfactory) (SCN, 2004). In both instances, this would lead to a reduction of severity of diarrhoea.

With regard to impact on case-fatality rates in diarrhoea, most data come from studies in health services. Data from the SIAB reporting system in Ceará show that median hospitalization rates for dehydration in children in the districts went down considerably from 1999 to 2005. This would imply that diarrhoea has become less severe, either due to change in the disease pattern or improved rehydration practices.

A study of the introduction of ORT corners or treatment facilities in 11 hospitals found that overall diarrhoea case-fatality rates in the hospitals fell (WER, 1988). Similar reviews of effects of ORT corners in out-patient departments have shown significant reductions in admission rates suggesting fewer deaths among children coming to those hospitals (WER, 1984; WER, 1987, Hatch et al., 1990). Victora et al. found that diarrhoea admissions fell from 57% of infant hospitalizations in 1980 to 30% in 1990 in NE Brazil. None of the other major causes of death or admissions showed such a decline (Victora et al., 1996). The study also showed that there was no change in cases admitted in terms of severity of disease and treatment, implying that diarrhoea admission policies remained the same over the study period.

The ideal measurement of diarrhoea case severity would be community-based surveys of diarrhoea cases using the WHO classification on degrees of dehydration (WHO, 2005). As persistent diarrhoea and dysentery have particularly high mortality rates (Fauveau et al., 1992; Kotloff et al., 1999) it would also be useful to follow their development at population level.

Further efforts should be made to explore the interaction between case-fatality rates and overall mortality from diarrhoea. The need for enlightenment on this issue is particularly relevant if the absolute number of child deaths has been reduced from around 4.6 million in 1982 to approximately 2.0 million in 2000 in LMC while the child population in the same countries has increased from 391 to 553 million (U.S. Census Bureau, 2007). Given the limited change in diarrhoea morbidity in the same time period this suggests a remarkable reduction of case-fatality rates over 20 years of 69%.

There is a gap of knowledge on the development of case-fatality rates in developing countries which today prevents us from making robust conclusions on the reasons for the significant public health improvements that diarrhoeal diseases control appear to represent. Clearly, it should be a priority to fill this knowledge gap through further research.

5.3.5 Implications for Disease Control

Improved case management through ORT has been seen as a fairly simplistic intervention (Gerlin, 2006) but findings in this thesis support other evidence that adoption and effective use of ORT is more complicated than expected. The finding has implications not only for diarrhoea control but also for other simplified interventions aimed at households and primary care providers, such as control of Acute Respiratory Infections (ARI) (WHO, 2004a; Kallander, 2005), control of malaria (Morel et al., 2005; WHO, 2006b), HIV/AIDS control (UNAIDS, 2006) and Integrated Management
of Childhood Illness (IMCI). Such interventions should be compatible with and build on local expectations, needs, priorities and constraints. This standpoint finds support in recent research from Uganda (Nsungwa-Sabiti et al., 2004; Nsabagasani et al., 2007) and Mali (Ellis et al., 2007). The problem the intervention addresses must be seen as important by people in the community and they must feel that the time and money they have to invest in it is worth the benefits it brings. Philipson and Posner expressed this in their book on HIV/AIDS control in 1993 “... the standard epidemiological approaches fail to consider the role of incentives in shaping private responses both to the communicable disease itself and to programs aimed at controlling it” (Philipson & Posner, 1993). Health professionals on their side must feel that the intervention is in line with the paradigm that they have been trained in, and that it contributes positively to their performance as judged by superiors, colleagues, their clients and the community (Rowe et al, 2005). Research for improved disease control should focus on these factors (Berman et al., 1994)

Factors like education and general awareness of health issues in the community matter to behaviour change. Such factors in combination with well trained and motivated health professionals in a functioning health system will prepare people to be receptive to adequate measures and messages for diarrhoea treatment and control. Short-cuts to public health gains may be possible but universal, sustainable coverage of interventions cannot be reached without such a framework in place. A comprehensive approach to diarrhoeal diseases control will ensure that control efforts support the achievement of the three key MDGs that relate to diarrhoea.

However, strong commitment in health services is not enough. Comprehensive development is needed to reduce diarrhoea morbidity. Accelerated efforts to diarrhoea disease control will require collaboration across sectors. Specific interventions that are directly beneficial to diarrhoea control, like improved water and sanitation, need to be backed by a general rise in education and socio-economic conditions.
CONCLUSIONS AND POLICY IMPLICATIONS

This thesis has documented:

- progress in diarrhoea control in LMC over a 20 year period;
- still, significant problems in adopting and practicing ORT at household level in NE Brazil and in LMC;
- established diarrhoea case management in primary health services in NE Brazil in 1989 but also problems in implementation of such management;
- limited reduction in diarrhoea morbidity in a state in Brazil from 1998 to 2005;
- little association between disease determinants and diarrhoea morbidity in a state in Brazil;
- methodological problems and challenges in data collection and programme evaluation, especially with regard to household surveys;
- possible discrepancies in data on morbidity, case-management and mortality from LMC.

From the findings it can be concluded that policies for diarrhoea control should be more focussed on the actual case management practices and perceptions among caretakers and health workers. ORT use and proper case management need to be improved to reduce diarrhoea mortality further. Interventions for disease control should be compatible with and build on local expectations, needs, priorities and constraints. More research is needed to understand those factors before the launch of new initiatives and interventions. On-going interventions also need to be continuously assessed and studied in relation to both community members and health workers.

The findings also have implications for methodological research. Paper III showed the need for more in-depth studies of how to improve methods for data collection in households.

The thesis also points to need for better understanding of the interaction between diarrhoea mortality, case-fatality and diarrhoea morbidity.

At the moment it is unclear what route child health, including diarrhoeal disease control, will take in LMC. International attention in health development assistance has been concentrated on tuberculosis, malaria and HIV/AIDS (G8, 2006; Feachem & Sabot, 2006) and less on child health. The Integrated Management of Childhood Illness (IMCI) is being discussed as a possible way forward. Its consequences for each of the diseases it covers should be studied in more details. The IMCI implementation problems identified (Bryce et al., 2005b) also need to be better understood and corrected.

The issues raised by the findings in the thesis need urgent attention. Results suggest that annually, more than 300 million children in LMC do not get ORT or increased amounts of fluid during diarrhoea, and more than 200 million children get neither, putting them at high risk of premature death due to dehydration. Morbidity from diarrhoea in LMC also appears to be slow in declining. A review and possibly a reformulation of current policies for diarrhoea control are called for. Focus should be on establishing proper case
management of diarrhoea as routine practice both in households and in health services, identifying high-risk groups and vulnerable children, and in promoting further expansion of factors important to diarrhoea morbidity reduction. The latter would entail advancement of both proximal determinants, like water and sanitation, and distal, like female education and general socio-economic development. In conclusion, high priority should be given to diarrhoeal diseases control in low- and middle-income countries, especially in poor communities where diarrhoea still is a frequent and life-threatening condition to children.
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ANNEX 1

Low- and Middle-income Countries/Territories

Afghanistan; Algeria; Angola; Antigua and Barbuda; Argentina; Armenia; Azerbaijan; Bahamas; Bahrain; Bangladesh; Barbados; Belize; Benin; Bhutan; Bolivia; Botswana; Brazil; Brunei Darussalam; Burkina Faso; Burundi; Cambodia; Cameroon; Cape Verde; Central African Republic; Chad; Chile; China; Colombia; Comoros; Congo; Congo, Democratic Republic of the; Cook Islands; Costa Rica; Côte d’Ivoire; Cuba; Cyprus; Djibouti; Dominica; Dominican Republic; Ecuador; Egypt; El Salvador; Equatorial Guinea; Eritrea; Ethiopia; Fiji; Gabon; Gambia; Georgia; Ghana; Grenada; Guatemala; Guinea; Guinea-Bissau; Guyana; Haiti; Honduras; India; Indonesia; Iran (Islamic Republic of); Iraq; Israel; Jamaica; Jordan; Kazakhstan; Kenya; Kiribati; Korea, Democratic People’s Republic of; Korea, Republic of; Kuwait; Kyrgyzstan; Lao People’s Democratic Republic; Lebanon; Lesotho; Liberia; Libyan Arab Jamahiriya; Madagascar; Malawi; Malaysia; Maldives; Mali; Marshall Islands; Mauritania; Mauritius; Mexico; Micronesia (Federated States of); Mongolia; Morocco; Mozambique; Myanmar; Namibia; Nauru; Nepal; Nicaragua; Niger; Nigeria; Niue; Occupied Palestinian Territory; Oman; Pakistan; Palau; Panama; Papua New Guinea; Paraguay; Peru; Philippines; Qatar; Rwanda; Saint Kitts and Nevis; Saint Lucia; Saint Vincent/Grenadines; Samoa; Sao Tome and Principe; Saudi Arabia; Senegal; Seychelles; Sierra Leone; Singapore; Solomon Islands; Somalia; South Africa; Sri Lanka; Sudan; Suriname; Swaziland; Syrian Arab Republic; Tajikistan; Tanzania, United Republic of; Thailand; Timor-Leste; Togo; Tonga; Trinidad and Tobago; Tunisia; Turkey; Turkmenistan; Tuvalu; Uganda; United Arab Emirates; Uruguay; Uzbekistan; Vanuatu; Venezuela (Bolivarian Republic of); Viet Nam; Yemen; Zambia; Zimbabwe

Source: UNICEF, 2006