Donau-Universität Krems
Universität für Weiterbildung

IN COOPERATION WITH THE VIENNESE SCHOOL OF OSTEOPATHY

OSTEOPATHIC MANIPULATIVE THERAPY AS ADJUNCTIVE TREATMENT ON HOSPITALIZED CHILDREN WITH PNEUMONIA IN CAMBODIA

A RANDOMIZED CONTROLLED PILOT STUDY

MASTER THESIS FOR OBTAINING THE ACADEMIC DEGREE

MASTER OF SCIENCE

IN THE STUDY PROGRAMME OSTEOPATHY

SUBMITTED BY
Theresia Orsini-Rosenberg

DEPARTMENT FOR HEALTH, SCIENCE AND BIOMEDICINE
AT DANUBE UNIVERSITY KREMS

Advisor: Mag. Dr. Astrid Grant-Hay
Advisor: Raimund Engel, MSc D.O., Director of the Viennese School of Osteopathy

SIEM REAP / HAMBURG, MAY 2016

STATUTORY DECLARATION

I, Theresia Orsini-Rosenberg, born May 28th, 1984 in Vienna hereby declare,

that I have written my Master Thesis myself, have not used other sources than the ones stated and moreover have not used any illegal tools or unfair means,

that I have not publicized my Master Thesis in my domestic or any foreign country in any form to this date and/or have not used it as an exam paper,

that, in case my Master Thesis concerns my employer or any other external cooperation partner, I have fully informed them about title, form and content of the Master Thesis and have his/her permission to include the data and information in my written work.

Date and Signature

_____

ACKNOWLEDGEMENTS

I would like to acknowledge the Angkor Hospital for Children in Siem Reap / Cambodia for their collaboration and their support of this study. Especially the staff of the physiotherapy department, Mr. Tan Sethy (TS), Mr. Sothorn, Mrs. Kimlay and Mrs. Sreyphos for assisting in the clinical research and helping out wherever they can. – "Awcun makaplou."

Furthermore, I would like to thank all the participants and their caretakers who took part in the study, for their patience and trust.

A big thank you goes to my supervisors, Mag. Dr. Astrid Grant-Hay and Raimund Engel who always found time to kindly answer my e-mails, at all times took my questions seriously, mentally and professionally supported me and guided me throughout this learning experience.

To my incredibly helpful friend Jenny, who donated parts of her holidays and lots of her precious time to teach me pretty much everything in statistics and read through my results. I could not have done it without you!!!

Of course all my fantastic proof-readers and patient helpers deserve to be acknowledged. @ Micky, Louise and Teresa: you were with me during the rather stressful final spurt and did a fantastic job!

Thank you WSO - all the staff and teachers, for patiently teaching me over the last eight years and helping me become the person I am now. – One of the lucky people who loves her job!

I would never have come that far without the continuous, generous support of my father who – as a matter of course – funded and encouraged all my years of studying and much more. Thank you, Papi!

And last but not least to my fiancée Friedrich: thank you for patiently teaching me how to professionally use Excel (and even Word), reading through parts of my thesis again and again, coming with me to Cambodia, being there whenever I need you and supporting me with your very rational advice. I love you!

ABSTRACT (ENGLISH)

OBJECTIVE: The study was designed as a randomized, controlled pilot study to assess the efficacy of Osteopathic Manipulative Treatment (OMT) as an adjunctive treatment to conventional clinical care only (CCO) in children < 5 years, hospitalized with pneumonia.

METHODS: 41 eligible subjects were randomly allocated to an OMT (n=20) and a CCO group (n=21). All subjects received conventional care for pneumonia. Patients in the OMT group additionally received OMT once daily, 5-times per week for approximately 15 minutes until discharge, study withdrawal or death. Primary outcomes were length of hospital stay (LOS), duration of fever (DOF), duration of tachypnea (DOT) and time until oxygen saturation is >90% (SatO2). 4 sub-groups were pre-defined to be analysed separately: radiographic pneumonia and WHO-defined clinical pneumonia only, ventilation support (VS) and no VS, chronic heart disease (CHD) and no CHD and CLD on admission and no CLD on admission. Value distribution was tested using the Shapiro-Wilk test. Chi-square tests, independent samples t-tests and non-parametric tests were conducted to determine significant differences between groups.

RESULTS: Although the mean and median values of LOS, DOF and SatO2 were shorter in the treatment group, no statistical significance was reached. A similar trend was also shown when comparing the subgroups. However, analysis of secondary outcomes found a significant difference in frequency of nosocomial infection (NCI) between groups (OMT=0, CCO=4; p=0.04).

CONCLUSION: OMT may have an effect on the recovery of childhood pneumonia and was shown to reduce the risk of NCI. However, a larger study is needed to verify these preliminary results.

KEY WORDS: osteopathic manipulative treatment, childhood pneumonia, nosocomial infection

ABSTRACT (GERMAN)

ZIEL: Diese Studie ist eine randomisierte, kontrollierte Pilotstudie mit dem Ziel die Wirksamkeit von Osteopathie als Zusatztherapie, neben der herkömmlichen, klinischen Behandlung bei Kindern unter 5 Jahren mit akuter Lungenentzündung zu untersuchen.

METHODIK: 41 geeignete Testpersonen wurden randomisiert und in eine Kontroll- (CCO) und eine Interventionsgruppe (OMT) eingeteilt. Alle Teilnehmer erhielten eine herkömmliche, klinische Behandlung gegen Lungenentzündung. Patienten der OMT Gruppe erhielten zusätzliche osteopathische Behandlungen. Primäre Ergebnisparameter waren Dauer des Krankenhausaufenthaltes (LOS), Fieberdauer (DOF), Dauer der Tachypnoe (DOT) und die Anzahl der Tage bis die Sauerstoffsättigung >90% betrug. 4 Untergruppen wurden im Vorhinein definiert. Hierfür wurden die Ergebnisse von Testpersonen mit und ohne einem Lungenröntgenbefund, mit und ohne Beatmungshilfe, mit und ohne zusätzlicher Herzerkrankung sowie mit und ohne zusätzlicher Lungenerkrankung nochmals getrennt betrachtet. Die Normalverteilung der Werte wurde mittels des Shapiro-Wilk Tests getestet. Chi-Quadrat Tests, t-Tests bei unabhängigen Stichproben und nicht-parametrische Testverfahren wurden angewandt.

ERGEBNISSE: Die Analyse zeigte einen signifikanten Unterschied zwischen den beiden Testgruppen bezüglich der Häufigkeit von NCI (OMT=0, CCO=4; p=0.04). Außerdem zeigten Vergleiche zwischen Mittel- und Medianwerten eine Verringerung von LOS, DOF und SatO2 in der Interventionsgruppe, allerdings ohne statistischer Signifikanz. Ähnliche Ergebnisse fanden sich auch bei der Analyse der einzelnen Subgruppen.

FAZIT: Osteopathie könnte einen Einfluss auf die Genesung von Kinder mit Lungenentzündung haben. Außerdem zeigt diese Studie, dass Osteopathie das Risiko nosokomialer Infektionen verringert. Um diese vorläufigen Ergebnisse zu bestätigen und weiterzuführen sind größere Studien dringend empfohlen.

SCHLÜSSELWÖRTER: Osteopathie, akute Lungenentzündung, Kinder, nosokomiale Infektion

TABLE OF CONTENTS

1. INTRODUCTION

Despite improvements in the therapy and application of antibiotics, pneumonia is still the reason for 15% of all deaths worldwide of children under 5 years in 2015 (World Health Organisation, 2015). Although it is a disease with large burden, serious gaps still remain in our knowledge about pneumonia in children (Bradley et al., 2011). Conventional antibiotic therapy may be enhanced by adjunctive non-pharmacological treatments. The evidence for chest physiotherapy and early mobilization as viable adjunctive treatments are conflicting though (Balachandran, Shivbalan, & Thangavelu, 2005; Paludo et al., 2008).

In the past, Osteopathic Manipulative Medicine (OMM) was built upon the reports of successfully treating systemic diseases, such as epidemic influenza and pneumonia (Hruby & Hoffman, 2007; Riley, 1951, 2000; Smith, 2000). Already the founder of Osteopathy, Andrew Taylor Still describes important structures to be treated in patients with pneumonia (Still, 1910). Many years later, the "Multicentre Osteopathic Pneumonia Study in Elderly" (MOPSE) (Noll et al., 2010), a thorough and extensive multi-institutional clinical trial to evaluate the efficacy of Osteopathic Manipulative Treatment (OMT) in the treatment of pneumonia in elderly patients, provided us with first results: In their per-protocol analysis, they found a significant decrease in hospital length of stay (LOS), duration of intravenous antibiotics and respiratory failure comparing the OMT to a conventional care only (CCO) group.

So far, no randomized clinical trial has ever successfully studied the efficiency of adjunctive OMT on hospitalized children with pneumonia. Two studies previously applied OMT on children with pulmonary diseases. The first attempt was conducted by Watson and Percival (1939) but the results were never published due to an inconclusive sample size. A second study was performed in the sixties on children with various pulmonary infections. The standardized OMT protocol solely included one technique, called the rib-raising technique, which was able to reduce the mean LOS in the OMT plus antibiotics group, in comparison to the the group only receiving antibiotic treatment or the group receiving only OMT (Kline, 1965). Therefore, the assumption that OMT can have a positive influence on children suffering from pneumonia seems plausible. Due to their continuously developing and changing body and mind, children are easily adaptable and therefore well responding to OMT (Carine, Mills, & Frymann, 2010). It is still reasonable to presume though, that infants in an acute stage of disease may be too fragile for additional treatments. On the other hand, reducing LOS in such fragile patients is a primary medical aim, considering the danger of nosocomial infections. Thus, a thorough clinical trial to assess the efficiency of OMT as an adjunctive treatment on children hospitalized with pneumonia seems to be essential.

1.1. MOTIVATION

The clinical trial of this study was performed in cooperation with Angkor Hospital for Children (AHC) in Cambodia to help filling the research gap mentioned above. The author's motivation to conduct this research at AHC, Cambodia and not at any other hospital was based on three facts: Cambodia's urgent need for medical care improvement, AHC's well situated teaching and research surrounding and the author's prior employment at AHC as well as personal involvement in the country.

CAMBODIA is a country marked by its turbulent history: Being Southeast Asia's largest empire in the 12th, 13th and 14th century, a long series of wars with neighbouring countries led to its first big fall in the 15th century. Violent centuries followed until the French colonisation in 1863. When Cambodia gained independence from France mid of the 20th century, it became a constitutional monarchy with an auspicious future. However, the rise didn't last long. In the seventies, the Khmer Rouge came to power and tried to rebuild the country's agriculture on the model of the 11th century, discarded Western medicine and ended anything considered Western. An estimated number of two million people were killed – about a quarter of the entire population. After the liberation from this terrifying regime in the late 1970s, more than ten years of civil war followed and continued the destruction of the already blown up country. In 1991 peace was finally established and a government was elected. (Chandler, 2008) Until today, the country is still facing numerous challenges and social issues, including severe poverty (Thul, 2014), corruption, low human development (Transparency International, 2013), a high prevalence of hunger (Grebmer von et al., 2013) and a major lack of medical care facilities (Peters et al., 2008).

In 1999, the ANGKOR HOSPITAL FOR CHILDREN was founded as a non-profit paediatric hospital to provide free, quality health care to children in Siem Reap, Cambodia. The hospital offers inpatient and outpatient care, surgical services, emergency services, intensive care treatment, dental care, ophthalmologic services and antiretroviral HIV therapy to over 150,000 children each year. Among other units, it also has a physiotherapy department, radiology services, a laboratory and a research department. Besides providing quality health care, AHC is officially recognised as a teaching hospital since 2005 offering trainings to health care workers all over the country. ("Angkor Hospital for Children," 2016)

From 2009 to 2011 the author was based at Angkor Hospital for Children helping to develop the physiotherapy department and working closely with the local medical staff and research team. During this three-year period, the high incidence of pulmonary diseases in hospitalized children was remarkable and with pneumonia as the primary cause of mortality in 28% of all deaths at AHC (n=700, three-year mortality audit), improving the treatment seemed vital.

Although evidence for chest physiotherapy is conflicting, it is the main adjunctive therapy for pneumonia prescribed by AHC's doctors and administered by the physiotherapy team. Yang et al.'s review (2013) about the evidence of chest physiotherapy in adults gave the author the first hint of a possible positive influence of OMT on pneumonia and triggered further research. So

far, OMT is not taught in Cambodia or elsewhere in Southeast Asia and is therefore not part of the medical care. AHC, as an officially recognized teaching hospital to improve medical skills seems to be a suitable institution to give Cambodia a first insight of OMT.

1.2. LIMITATIONS

One of the key decisions about the set-up of this study was how broadly to target cases of pneumonia being hospitalized in Angkor Hospital for Children. Considering the fact, that children in developing countries with a chronic disease are more likely to develop severe pneumonia (Rudan, Boschi-Pinto, Biloglav, Mulholland, & Campbell, 2008), the study was designed without excluding children with chronic diseases to have a most realistic sample size. Limitations had to be made with hospital-acquired pneumonia. Since the pathogens of pneumonia acquired in the hospital may be difficult to control, children suffering from a possibly hospital-acquired pneumonia were excluded from this trial. Therefore, this study solely focuses on children with community-acquired pneumonia (CAP) as described in Chapter 2.2.

1.3. STRUCTURE OF THE THESIS

For a better understanding of the topic, the next chapter will first discuss some theoretical aspects based on a literature review followed by a definition of the research question and a description of the study's methodology. Furthermore, results of the statistical analyses will be presented and discussed before the author ends with a final conclusion.

2. LITERATURE REVIEW

The following chapter serves a twofold purpose: Firstly, it intends to create a definitional and theoretical foundation for the subsequent elaborations in this paper and secondly it discloses the current state of knowledge in the field of osteopathic therapy in respect to pneumonia. On the basis of this literature review possible research gaps are to be identified in order to enable the development of a precise and relevant research question in the ensuing chapter 3. After a brief overview of the methodology used for this literature review, it does so by clarifying childhood pneumonia as a general phenomenon and subsequently discussing the osteopathic approach to the respiratory system.

2.1. METHODOLOGY OF THE LITERATURE REVIEW

To guarantee the scientific value of a literature review, it is a necessity to ensure the transparency and replicability of the search process for the identification of relevant literature (Torraco, 2005). Following this train of thought, the literature review in this paper leans on the guidelines by vom Brocke et al. (2009), as well as Webster und Watson (2002).

The databases Pubmed, Ovid, Web of Science and Google Scholar were considered appropriate and were thus consulted for this literature review. The literature search is based on a systematic approach, which was implemented through the combination of various key words classified as relevant. This search grid was applied to all databases in an identical manner. The keywords used include “Osteopathic manipulative treatment”, “pneumonia”, “children”, “childhood pneumonia” and “community-acquired pneumonia”. In a further step, a forward and backward search was performed in order to find sources referred to by the identified literature, as well as to locate sources which the identified literature referenced. The forward search was performed by the use of the Web of Science and the quotation database of Google Scholar. Sources were only taken into account if they were related to the subject of this thesis.

2.2. CHILDHOOD PNEUMONIA

According to the World Health Organization (WHO) (2015), childhood pneumonia is defined on the basis of clinical signs, such as cough or difficulty in breathing and respiratory rate. The presence of further signs and symptoms like central cyanosis, difficulties in drinking and lower chest wall in-drawings can but don’t have to occur in such patients and are used to specify the severity of pneumonia. Fever might be considered as a screening sign, but with not enough sensitivity and specificity for pneumonia (Scott et al., 2012). Radiographic detections of a parenchymal consolidation may help diagnosing the infection. However, besides the fact that radiological facilities are not available worldwide, many children with clinical signs of pneumonia but no abnormalities on the chest X-ray still respond to antibiotics (Scott et al., 2012).

The specification “community-acquired pneumonia" (CAP) is clinically characterized by the occurrence of signs and symptoms of a lung infection transmitted and acquired outside of the hospital (Don, 2009). In contrast, hospital-associated pneumonia is characterized by the same symptoms and signs but often caused by different pathogens with greater representation of multiple antibiotic resistance (Iregbu & Anwaal, 2007). The objective of this study is to evaluate the efficiency of OMT on children with community-acquired pneumonia. Therefore children with an overnight admission to any hospital within the last 14 days prior to this study have been excluded from the trial.

2.2.1. EPIDEMIOLOGY

Prevalence of pneumonia decreases when children get older. Two studies from the 1980s showed this among the Finnish as well as the American population (Jokinen et al., 1993; Murphy, Henderson, Clyde, Collier, & Denny, 1981). Jokinen et al (1993) also found a strong male incidence in children younger than 5 years (11.2/1000 males and 5.7/1000 females).

The overall observed hospitalization rate for childhood pneumonia in America und Europe is about 1-4/1000 per year (Farha & Thomson, 2005; Senstad et al., 2009). In developing countries pneumonia is not only more common than in the developed world (Figure 1) (Rudan et al., 2008) also pneumonia is known to be more severe and have a higher mortality rate among children (Bulla & Hitze, 1978; Rudan et al., 2008). According to Rudan et al. (2008), Cambodia is among the countries with the highest incidence of childhood clinical pneumonia (0.41-0.50 episodes per child-year) world wide (Figure 1). The mortality rate caused by pneumonia in the South-East Asian Region alone is 19% of all children less than 5 years dying in this area (Figure 2).

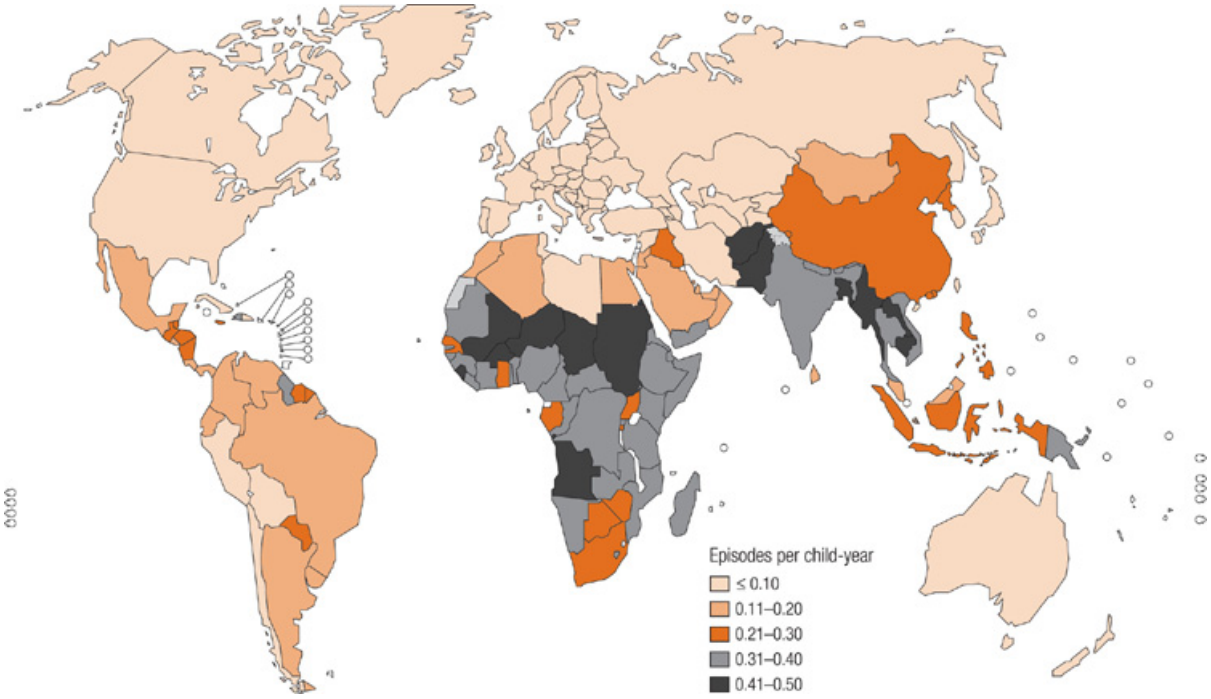

Figure 1: *Incidence of childhood clinical pneumonia at the country level: In 2000 more than 95% of about 156 million new episodes occurred in developing countries (Rudan et al., 2008, p. 3).*

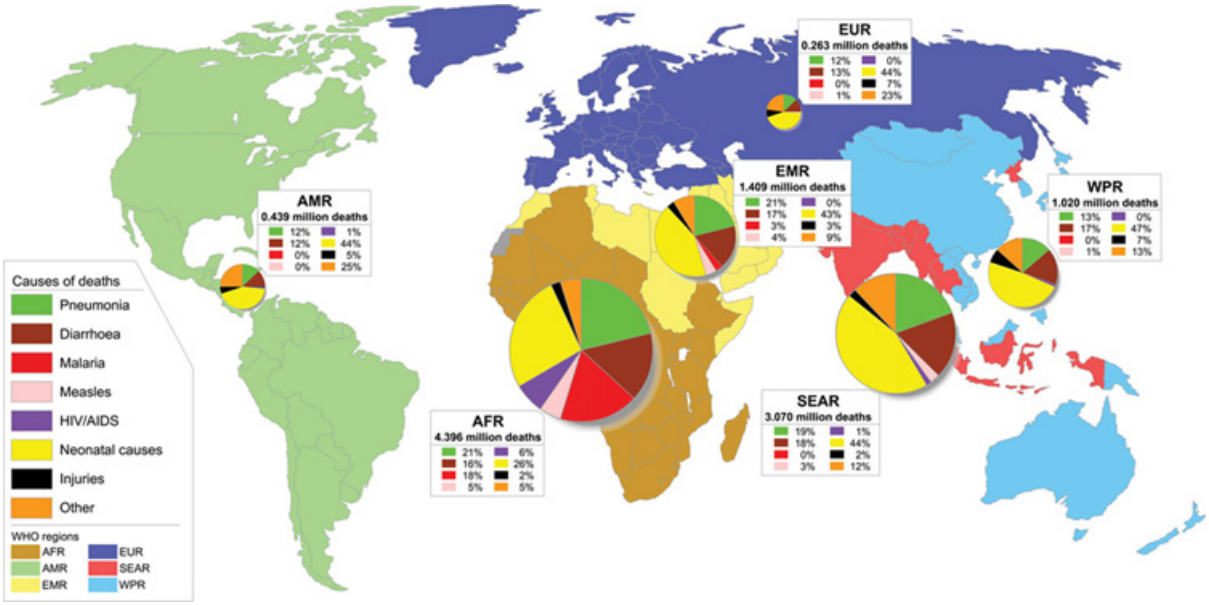

Figure 2: *Distribution of deaths from pneumonia and other causes in children aged less than 5 years, by WHO region (Rudan et al., 2008, p. 5).*

2.2.2. CAUSES AND RISK FACTORS

For a better understanding of the high incidence and severity of pneumonia in <5 year-old children in developing countries it is important to understand causes and risk factors that lead to these infections. However, thorough studies looking at pneumonia risk factors, especially in third world countries, are remarkably rare. Recurrent respiratory infections (RRI) and the history of episodes of wheezing or otitis media until the age of 2 years were found as possible risk factors in the Northern European paediatric population (Heiskanen-Kosma, Korppi, Jokinen, & Heinonen, 1997). Furthermore, it was found that in mild climates, pneumonia is more common in colder month, probably due to the frequent changes from dry indoor to cold outdoor air, as well as increased droplet spread of respiratory pathogens due to crowding (Durbin & Stille, 2008). The only paper looking into risk factors affecting the incidence of community-acquired childhood pneumonia in developing countries was written by Rudan et al. (2008). Since pneumonia in children is caused by the exposure to different host-, environment- and infection-related risk factors, they established three categories: definite, likely and possible risk factors, which are shown in Table 1.

Table 1: *"Risk factors related to the host and the environment that impact on the incidence of childhood clinical pneumonia in the community in developing countries (Rudan et al., 2008, p. 8).*

DEFINITE RISK FACTORS	LIKELY RISK FACTORS	POSSIBLE RISK FACTORS
Malnutrition (weight-for-age z-score <-2)	Parental smoking	Mother's lack of education (bad nutrition, lack of basic health care, etc.)
Low birth weight (≤ 2500g)	Zinc deficiency	Day-care attendance
Non-exclusive breastfeeding (during the first 4 month of life)	Mother's lack of experience as a caregiver	Rainfall (humidity)
Lack of measles immunization (within the first 12 month of life)	Concomitant diseases (e.g. diarrhoea, heart disease, asthma)	High altitude (cold air)
Indoor air pollution		Vitamin A deficiency
Crowding		Birth order
		Outdoor pollution

2.2.3. PATHOGENESIS

Very often pneumonia follows an upper respiratory tract infection (URTI) which was caused by microorganisms transmitted through person-to-person droplet spread. After the initial colonization of the upper airways, organisms may be further inhaled, causing an infection of the lung parenchyma. Before this actually happens the pathogens, such as viral or bacterial agents, have to pass multiple barriers of the body's pulmonary host defence system. These natural protections against pneumonia include saliva, nasal hairs, the mucocilary escalator, the epiglottis and the cough reflex as well as immunoglobulin A and G, surfactant and fibronectin, which play an important role in microbial killing. The most common etiologic bacterial agents causing pneumonia in <5 year-old children are streptococcus pneumoniae and gram-negative bacilli. A viral pneumonia might be caused through chlamydia trachomatis, the respiratory syncytial virus (RSV), parainfluenza, the human metapneumovirus or the rhinovirus. (Durbin & Stille, 2008) These are only examples and a lot of research has been done on pathogens but getting deeper into this matter would exceed the scope for this thesis.

2.3. AN OSTEOPATHIC APPROACH ON THE RESPIRATORY SYSTEM

2.3.1. THE OSTEOPATHIC PHILOSOPHY

The Glossary of the Osteopathic Terminology (Weston et al., 2011, p. 33) defines the osteopathic philosophy as "a concept of health care, supported by expanding scientific knowledge that embraces the concept of the unity of the living organism's structure (anatomy) and function (physiology). Osteopathic philosophy emphasizes the following principles:

1. The human being is a dynamic unit of function
2. The body possesses self-regulatory mechanisms that are self-healing in nature
3. Structure and function are interrelated at all levels
4. Rational treatment is based on these principles"

To enhance the patient's capacity to maintain or restore optimal function and health it is important to focus not only on dysfunctional or impeding functions, but also to acknowledge the physiologic body functions, which can help maintaining or restoring the patient's health. The following five basic integrative body functions have been summed up in osteopathic literature: posture and motion, respiratory and circulatory factors, metabolic processes, neurologic integration and psychosocial / behavioural elements (Seffinger et al., 2011).

2.3.2. NORMAL FUNCTIONAL RESPIRATION

Kuchera (1994) stated: "Respiration is a dynamic orchestration involving coordinated reflex neural activity, abdominal diaphragmatic and various other muscular contractions, motion of fascial planes, and the movement of 146 joints of the body." Its purpose is to supply each cell of the body with oxygen and eliminate carbon dioxide. Efficiency of this "orchestration" is not

only necessary for good respiration, but also produces important pressure gradients between the thoracic and the abdominal cavities. This cyclic pressure acts as a lymphatic and venous pump and hosts biochemical and physical reactions which occur in the blood stream during respiration.

Neural reflex activity is the motor of the whole respiratory function. The solitary nucleus of the respiratory centre in the medulla is informed of the collapse of the air sacs by the visceral afferent fibres of the vagal nerve (X). A reflex arch from the solitary nucleus to the mid-cervical area (C3-C5) follows and produces a contraction of the diaphragm via the phrenic nerve. To prevent a thoracic collapse through the contraction of the diaphragm, the somatic intercostal nerves (T1-T12) activate the intercostal muscles to stabilize the intercostal space. As soon as the air sacs are filled, visceral afferent reflexes inhibit the solitary nucleus again and cause a relaxation of the diaphragm and the intercostal muscles. The respiratory epithelium is also reliant on a good balance between sympathetic and parasympathetic nerve impulses. The parasympathetic influence via the vagal nerves is dominant in a normal functioning lung though. It produces the clear, saliva-like (but sticky) mucous blanket (Kuchera & Kuchera, 1994).

If all the points mentioned above are to be accomplished with optimal clinical effect, the interstitial tissue environment has to be as free from congestion as possible to be able to provide good circulation and effective neural reflex action. Osteopathic manipulative treatment (OMT) has been researched to affect the pulmonary environment through somato-somatic and somato-visceral reflexes (Noll, Johnson, Baer, & Snider, 2009). Furthermore, it has also been shown to affect the musculoskeletal mechanics involved in breathing, respiration and lymph flow (Creasy, Schander, Orlowski, & Hodge, 2013; Hodge, 2012).

2.3.3. PATHOPHYSIOLOGIC REFLEX RESPONSES DURING INFECTION

Infection, whether viral or bacterial, produces a local irritation of the bronchial epithelium which may spread into parenchymal lung tissue. Thus, visceral afferent nerve endings are stimulated in the area of the tissue injury which leads to a visceral afferent shelling of the spinal cord from T1-6. As a result, sympathetic hyperactivity can be found in the related lung tissue, resulting in hypoperfusion due to increased vasoconstriction. Another effect of hyper-sympathetic activity is an increase of goblet cells in the bronchial epithelium. Therefore, not only more mucus is produced, but the mucus becomes thick, profuse and difficult to cough up. Also the parasympathetic system gives a response to pathological occurrences of the lung tissue. Since the Hering-Breuner reflex mechanism cannot distinguish between air sacs filled with air and filled with fluid, the vagal nerve keeps sending wrong information to the respiratory centre. At the same time the carotid body, which is sensitive to carbon dioxide concentration in the blood, tells the respiratory centre that more oxygen is needed and the abdominal diaphragmatic rate should be increased. The result is often shallow and rapid breathing. These pathophysiologic changes also stress the mechanical and physical components of respiration. The relative immobility of the ribs and spine as well as the tissue resistance caused by the lung congestion, irritate the mechanics of the abdominal diaphragm causing a strain of its attachments to the lower six ribs and the thoracolumbar junction. A flattening of the diaphragmatic dome may be found as a result. Since a well-domed diaphragm produces effective changes in volume between the thoracic and the abdominal cavity, it is a major pump for the lymphatic flow (Table 3). The flattened diaphragm leads to a serious decrease of volume displacement and therefore a decreased lymphatic flow, which at the end causes even more congestion of tissues. (Beal & Morlock, 1984; Kuchera & Kuchera, 1994)

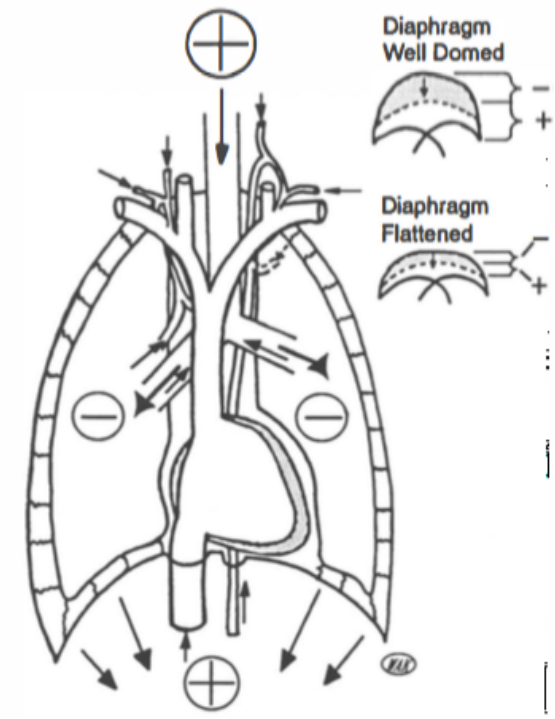

Figure 3: The diaphragm as a lymphatic pump (Kuchera & Kuchera, 1994).

2.3.4. SOMATIC DYSFUNCTIONS CORRELATING PNEUMONIA

Already in the early twentieth century, osteopathic physicians in the Unites States correlated pulmonary diseases with atypical structural findings, which were later named somatic dysfunctions (SDF). They mainly consisted of positional asymmetry of bony landmarks, limited joint motion, congested tissue, tight muscles and palpatory tenderness (Noll, Degenhardt, Fossum, & Hensel, 2008). Lower respiratory tract infections, for example, routinely corresponded with dysfunctions from T1 to T10 including the associated ribs. Furthermore, dysfunctions of the

cervical spine, especially C0/C1 (vagal nerve) and C3-C5 (phrenic nerve), the cervicothoracic junction, the first ribs and the clavicles (thoracic inlet) were associated specifically with pneumonia (Cole, 1961; Cole & Pearson, 1949). Limited by a lack of objective instrumentation in the early twentieth century, physical examination and repeated observation were the primary methods of osteopathic physicians. Therefore, numerous studies have been published on pulmonary diseases correlating SDF (Corbin, 1918; Hoyt, 1947; Peck, 1948; Soden, 1934). Although authors debated details of anatomy and pathophysiologic mechanisms, certain theories were common. Noll et al. (2008) summarized a list of commonly described findings based on a thorough historical literature review from 1901 -1951 (**Table 2**). Already during this time, osteopathic physicians assumed, that somatic dysfunctions impede the patient's ability to recover from infectious diseases through subsequent mechanical, neurological and circulatory changes as mentioned in chapter 0.

Table 2: *Summary of commonly described SDF in patients with pneumonia based on a historical literature review from 1901-1951(Noll et al., 2008, p. 520).*

Cervical Region *	Thoracic Region*	Others*
➢ Occipital lesions ➢ Upper cervical spine ➢ Contracted accessory muscles of respiration	➢ Clavicles ➢ Rib lesions and rigid intercostal muscles ➢ Thoracic lesions ➢ Upper thoracic spine (T1-T8) and its rigid muscles ➢ T10-T12 region and its rigid muscles ➢ Thoracolumbar junction (T10-L2) ➢ Rigid diaphragm	➢ Lymphatic congestion ➢ Lumbosacral lesion

**Findings were not necessarily specified on segments but roughly attributed to a region.*

2.3.5. OSTEOPATHIC MANIPULATIVE TREATMENT FOR PNEUMONIA

Noll et all (2010) define Osteopathic Manipulative Treatment (OMT) as a non-pharmacologic manual therapy developed in the late nineteenth century by AT Still. It was already used before the application of antibiotics and includes several manipulative techniques with the aim to enhance host defences and physiologic function (Facto, 1947; Kimberly, 1980). While osteopathic physicians of the early twentieth century researched on SDF correlating pneumonia, they also debated useful techniques to treat pulmonary infections (Corbin, 1918; Hoyt, 1947; Peck, 1948; Soden, 1934; Still, 1910). More recent research on OMT in patients with pneumonia mostly builds up and therefore corresponds with the anecdotal literature when it comes to the choice of techniques. Most studies focused on adults rather than children suffering from pneumonia

and described soft tissue techniques on the cervical and thoracic spine, rib raising, doming of the diaphragm, suboccipital inhibition, myofascial release of the thoracic inlet and lymphatic pump techniques as most commonly used techniques (Creasy et al., 2013; Noll et al., 2008; Yao, Hassani, Gagne, George, & Gilliar, 2014). Early osteopathic physicians also cited the need to relieve tissue tightness in the area of the the thoracolumbar junction to stimulate the innervating nerves of liver and kidney and therefore improve the removal of circulatory waste products (Corbin, 1918; Hoyt, 1947; Peck, 1948; Soden, 1934; Still, 1910). This theory has not been included in any of the more recent studies.

Only two papers were found, focusing specifically on OMT techniques for children with pulmonary diseases. Watson and Percival (1939) performed the first attempt in 150 children hospitalized with bronchopneumonia in California, U.S.A. The children received ether a standardized OMT protocol with supportive care, or supportive care only. Furthermore, they included a third group of children (n=89) hospitalized with pneumonia who received an inoculate animal serum used for passive immunization plus supportive care. Similar to techniques used on adults, they conducted a standardized OMT protocol including soft tissue techniques on the cervical spine, inhibition of the paraspinal muscles, rib raising, intermittent suboccipital pressure and light stroking to the lower intercostal spaces as a lymphatic technique. Unfortunately, results of this study have never been published because the researchers thought that “too few cases had been accumulated to be conclusive” (Watson & Percival, 1939).

In the sixties, Kline (1965) evaluated the effect of OMT on 252 children hospitalized for various respiratory tract infections. He therefore, randomly assigned the subjects to an OMT group, an antibiotic group, or an OMT plus antibiotic group. All three groups received additional supportive care. OMT was applied via a standardized protocol solely consisting of the rib raising technique. Frequency and duration varied according to the patient’s age. The mean length of hospital stay was 6.3 days for the OMT group, 5.8 days for the antibiotic group and 4.8 days for the OMT plus antibiotic group.

Optimal duration and frequency of standardized OMT sessions are debatable and seem to differ between adults and children. Duration recommendations for adults varied between 10 minutes to 20 minutes (Facto, 1947; Noll et al., 2010, 2008) whereas no specific treatment duration has been mentioned in OMT protocols for children with infectious diseases (Kline, 1965; Watson & Percival, 1939). The typical recommended frequency for adults was two treatment sessions per day (Hammer, 1947; Noll et al., 2008; Still, 1910; Underwood, 1934) or even more for the seriously ill (Facto, 1947). However, in children the frequency mentioned in previous literature was depending on height of fever or age of the patient (Kline, 1965; Watson & Percival, 1939). Watson & Percival (1939)

In the past, research studies evaluating OMT for pulmonary diseases commonly used standardized OMT protocols without taking into consideration the unique nature of each individual. Only two pilot studies on elderly patients hospitalized for pneumonia considered specific OMT in addition to standardized OMT protocols. They therefore included a specialized osteopath,

who was instructed to provide one or more non-standardized treatment session during the hospital stay focusing on specific SDF unique to the patient (Noll, Shores, Bryman, & Masterson, 1999; Noll, Shores, Gamber, Herron, & Swift, 2000). Noll et al. (2000) found a significant 2-day difference in length of hospital stay (LOS) between the OMT group (6.6 days) and the light touch group (8.6 days). Based on this outcome, a multi-institutional clinical trial to evaluate the efficiency of OMT in the treatment of pneumonia in 406 elderly patients was designed (Noll et al., 2010). Patients were randomly assigned in a conventional care only (CCO), light-touch (LT) or OMT group. Using a standardized OMT protocol without additional OMT addressing specific SDF unique to the patient, the intention-to-treat analysis (ITT) did not indicate any improvements in designed outcomes between the OMT group and the control groups. However, per-protocol analysis (PP) found a significant reduction ($p=0.01$) in median LOS comparing the OMT group (3.5 days) versus the CCO group (4.5 days). Median duration of intravenous antibiotics and treatment endpoints (death or respiratory failure) were also significantly lower for the OMT group ($p=0.05$) versus the CCO group ($p=0.006$) (Noll et al., 2010).

3. OBJECTIVE, RESEARCH QUESTION AND HYPOTHESISES

This randomized controlled pilot study is designed to help filling the gap of research revealed in the previous chapter. Main objective is to determine the efficiency of OMT as adjunctive treatment on children younger than five years old with acute community-acquired pneumonia in Cambodia. Primary outcome measures include total length of hospital stay (LOS), total duration of fever (DOF), total duration of tachypnea (DOT) and time until oxygen saturation >90% (SatO2). Secondary outcome measures are mortality, frequency of nosocomial infections (NCI), and diagnosis of chronic lung disease (CLD) at discharge.

Based on the defined objective, the following RESEARCH QUESTION was determined:

DOES OMT AS AN ADJUNCTIVE TREATMENT TO CONVENTIONAL CLINICAL CARE, EFFECT RECOVERY FROM ACUTE COMMUNITY-ACQUIRED PNEUMONIA IN HOSPITALIZED CHILDREN IN CAMBODIA?

Therefore, two non-invasive treatment groups were designed and included in this trial:

1. CONTROL / CONVENTIONAL-CARE-ONLY (CCO) GROUP: patients in the control group received AHC's conventional care only (CCO) as defined in 4.5.1.
2. INTERVENTION / OMT GROUP: patients in the intervention group received full OMT as defined in 0, adjunctive to AHC's conventional care.

The following HYPOTHESIS was determined to help answering the defined research question:

THE NULL HYPOTHESIS states that there is no significant difference to be found in one or more of the measured primary and/or secondary outcomes comparing the intervention group (OMT) to the control group (CCO) while THE ALTERNATIVE HYPOTHESIS states there is a significant difference to be found in any of the measured primary and/or secondary outcomes comparing the intervention group (OMT) to the control group (CCO).

Outcomes of the two groups were compared after the last study subject was discharged and data collection was completed.

4. METHODOLOGY

4.1. STUDY DESIGN

The study was designed as a one-side-blinded, randomized controlled pilot trial at Angkor Hospital for Children, Cambodia. AHC's research committee and institutional review board (IRB) approved the study (s. APPENDIX A) Two co-researchers (TS. and CS.), staff from AHC's physiotherapy department were recruited to assist in the study.

4.2. RECRUITMENT, RANDOMISATION AND BLINDING

All patients admitted to AHC and diagnosed with pneumonia (World Health Organisation, 2015) by the receiving medical staff were - if needed - emergency treated and within 24 hours referred to one of the co-researches, who checked eligibility for the study. Once the participant was deemed eligible, the co-researcher informed the patient's caretaker of the study and handed over a standardized information sheet - both in Khmer language. Patients' caretakers were made aware that study involvement was voluntary and that they could refuse to answer any question or withdraw their child at any time. Furthermore, they were assured that enrolment into the study will not affect any other medical care their child receives from AHC. Caretakers did not receive any other incentive for enrolling their child in the study. After agreeing, two copies of a Khmer consent form were signed or thumb-printed by the caretaker, the enrolling co-researcher and a non-research witness. One consent form was handed over to the caretaker and one was confidentially kept in the patient's chart. Participants were then randomly allocated to the intervention or control group by opening identical, randomly shuffled, sealed envelopes by the same certified osteopath (author) who later administered OMT on the patients of the intervention group. Patients, caretakers, co-researchers and doctors were not informed about the allocation of each participant. Due to the design of the study, a double-blinded trail was not possible and no "sham" osteopathy was carried out. All outcome measurements were collected by the blinded co-researchers on a daily base and not by the administering osteopath. The information sheet and consent form are available in Khmer and English language in APPENDIX B. APPENDIX C includes the Case Report Form (CRF), the Daily Assessment Form, Therapy Form and Outcomes Summary Form.

4.3. ELIGIBILITY CRITERIA

Patients with ≥1 day and ≤5 years of age, admitted to AHC and presented with cough and/or difficult breathing with ether fast breathing (tachypnea) or chest wall indrawings and therefore diagnosed with pneumonia by AHC doctors were eligible to participate in this study.

Patients were excluded if they were suffering from lung abscess, tuberculosis, any kind of cancer or acute rib or other bone fractures. If symptoms were not present on day of admission or if the patient has been admitted overnight to any hospital within the last 14 days he was also excluded. Furthermore, patients whose primary caretakers could not speak or understand Khmer or English were excluded.

4.4. OUTCOME MEASURES

All outcome measures for this study were entered into Microsoft Excel and later on transferred into SPSS for statistical analyses. Baseline characteristics of the patients and their families were collected by the co-researchers. Outcome measures used to assess efficiency were taken hourly by non-research medical staff and noted in the charts. The daily peak value of each outcome measure was later on collected by one of the co-researchers.

4.4.1. BASELINE CHARACTERISTICS

Baseline characteristics were analysed in case of significant differences between the intervention and the control group. Collected data included age (years), gender, low birth weight (<2000g), prematurity (<37 weeks), maternal smoking, history of tuberculosis in the family, admitted to intensive care unit (ICU), malnutrition and chronic illness (including but not limited to CHD, HIV, CP, ITP and CLD).

4.4.2. PRIMARY OUTCOME MEASURES

Primary outcome measures included total length of hospital stay (LOS), total duration of fever (DOF), total duration of tachypnea (DOT) and time until oxygen saturation was more than 90% (SatO2).

Total LOS was measured in full days from day of admission until day of discharge, not including the day of discharge itself, based on the study of Noll et al (2010).

An axillary temperature greater than ≥38° Celsius was considered a fever (Noll et al., 2010). Temperatures were obtained from chart review. DOF was measured as the total number of consecutive days with a fever, including fever-free periods for less than 48 hours.

Tachypnea in this trial was determined at a respiratory rate of ≥59/min in infants younger than 6 moth, ≥52/min in those aged 6 through 11 month and ≥42/min in those aged older than 1 year (Taylor JA, Beccaro M, Done S, & Winters W, 1995). The patient's peak respiratory rate was obtained from chart review. Respiratory rate was only considered normal, once the patient was off invasive and non-invasive ventilation support and peak respiratory rate values were lower than the determined values. Tachypnea-free periods for less than 48h were included in the total calculation of DOT.

SatO2 was also obtained from chart review and was considered normal, once the patient had an oxygen saturation >90% without any additional ventilation and/or oxygen support for 24 hours or more (Cunningham et al., 2015).

4.4.3. SECONDARY OUTCOME MEASURES

Secondary outcome measures were mortality, frequency of nosocomial infections (NCI), total duration of intravenous (IV) and oral (PO) antibiotics and diagnosis of chronic lung disease (CLD) at discharge.

Mortality due to pneumonia and/or attributed mainly to respiratory failure (e.g. apnoea, failure to wean from ventilation, isolated severe respiratory acidosis) were clinically assessed by the medical team and recorded for the study.

NCI was defined as a new fever with increased white blood cell count or inflammatory markers (regardless of positive or negative microbiological cultures) after 48 hours or more with no fever.

Total duration of IV and PO antibiotics were obtained from chart review after the patient's discharge. Days of PO antibiotics, prescribed to continue at home, were included in the data collection.

Incidence of CLD was evaluated clinically on discharge and only used for this study if the patient had not had any signs of CLD on admission (e.g. previous hospitalizations due to respiratory problems).

4.4.4. PRE-DEFINED STUDY SUB-GROUPS

The following four subgroups were pre-defined to be analysed as part of the main study data and independently in case of differences in outcomes in these patients.

I. Subjects with radiographic findings of a parenchymal consolidation are to be separately analysed from those with pneumonia solely diagnosed on WHO clinical standards without any abnormalities on the chest X-ray (Radiographic pneumonia & WHO-defined clinical pneumonia only).
II. Subjects who have been on invasive ventilation or continuous airway pressure (CPAP) support for at least one day during their hospital stay are to be separately analysed from those who have not had any invasive or non-invasive ventilation support during their entire hospital stay (VS & no VS).
III. Subjects with clinical and/or radiological diagnosed cardiac failure secondary to structural heart disease are to be separately analysed from those without any signs of chronic heart disease. (CHD & no CHD)
IV. Subjects suffering from a chronic lung disease on admission including but not limited to asthma, broncho-pulmonary dysplasia, are to be separately analysed from those without any signs of a chronic lung disease. (CLD & no CLD)

4.5. PROCEDURES

All assessments occurred during the participant's inward hospital stay. Allocation of the patients in the different inward units (Intensive Care Unit, Inpatient Unit, Low Acute Unit, and Surgical Unit) was not controlled by this study's protocol but recorded on the patient's daily assessment form by the co-researchers. The co-researchers also collected baseline data of every eligible consenting patient on day of admission.

4.5.1. CONTROL GROUP: CONVENTIONAL CARE ONLY (COO)

Patients allocated to the control group received conventional clinical care according to AHC's standards, which was not controlled by this study's protocol but recorded on the patients' daily assessment form. Conventional care included but was not limited to microbiological cultures, chest X-ray, cardiovascular support, non-invasive / invasive ventilation, intravenous or oral antibiotics, and other medication such as anti-inflammatory painkillers, nasal drops and vitamin supplements as needed. AHC's standard care for patients on intensive care unit also includes postural drainage and mobilization every two hours performed by ether the responsible nurse or a physiotherapist. On less acute units, patients' caretakers were instructed to frequently change position and mobilize the child as tolerated. No further manual intervention, such as chest physiotherapy or OMT was administered on these patients.

4.5.2. INTERVENTION GROUP: OSTEOPATHIC MANIPULATIVE TREATMENT (OMT)

Patients allocated to the intervention group received the same conventional clinical care according to AHC standards as mentioned in chapter 4.5.1, also including postural drainage and mobilisation on intensive care unit and instructions to the caretaker on less acute units. In addition, they received OMT treatments for approximately 15 to 25 minutes, once daily, 5 times per week administered by the same specialized osteopath (author). Treatments started within the first 48 hours of admission and continued until hospital discharge, study withdrawal, or death.

The study's OMT protocol intends to be standardized enough for scientific reproducibility but flexible enough to be able to respond to each patient's unique structural findings. To achieve this balance, six techniques commonly used in the management of pneumonia have been chosen to be used during the treatments. Subjects are treated while lying in bed, half-sitting or sitting, depending on their condition.

All children in the OMT group receive a structural examination to identify unique somatic dysfunctions potentially related to pneumonia. At least one standardized technique has to be used in each therapy session of every patient but not every standardized technique has to be used in every patient on discharge. Although the techniques are standardized, each technique applied was dosed according to the patient's tolerance. In addition, non-standardized OMT is allowed at any time according to the child's needs.

The standardized OMT techniques have been mentioned and described in recent medical literature (Noll et al., 2008). In this study, some of them were adjusted for the better use in children.

While the patient was side-lying or in supine, the operator was always standing at the side or at the head of the bed. In half-sitting, techniques were performed while the child was sitting on the operator's or the caretaker's lab, leaning against the operator's or caretaker's thighs. If the patient's condition allowed unsupported sitting, the operator was ether sitting in front of, next to or behind the child. In some exceptions, the child was treated while breastfeeding. A summary of the techniques and their expected effects is provided in Table 3.

- **SOFT TISSUE** – The operator applies soft tissue techniques (kneading, massaging and stretching) to the cervical, thoracic and lumbothoracic paraspinal muscles. Attention may focus on areas of muscle tightness or spasm.
- **RIB RAISING** (Noll et al., 2008, p. 513) – The operator's hands are placed bilaterally under the patient's thorax while lying in supine or half-sitting. With a direct contact on the patient's rib angles the operator flexes the fingers and thus applies a lateral traction on the patient's rib angles. Maintaining this traction, the operator's hands slowly move towards the anterior side of the patient's thorax and therefore instigates a rising of the child's rib angles. Using the arms as a lever and the bed as a fulcrum, a gentle and steady rising and lowering of the rib cage may be conducted. After repeating this motion several times, the operator moves his hands further up the thoracic cage and repeats the technique until all the ribs are treated. Intension varies depending on the severity of restriction in different areas. The technique was adjusted to a sitting position if needed by placing the operator's hands unilaterally on the patient's ribcage with one operator's hand on the anterior ribcage of one side and the other hand on the dorsal ribcage of the same side. The operator would therefore sit next to the child and mobilize the ribcage towards a lateral-cranial-anterior direction. The technique is then repeated on the other side.
- **DOMING THE DIAPHRAGM** (adjusted technique) – The operator places her hands bilaterally on the patient's lower lateral ribcage applying soft compression to specifically focus on the dome of the diaphragm and determine the direction of the greatest freedom. Using an indirect myofascial technique, tissues are then moved in the direction of greatest ease to a point of balance and held there until a release of tissue tension is palpated.
- **SUBOCCIPITAL DECOMPRESSION** – The operator softly places her fingertips on the suboccipital muscles at the patient's cranial base and applies steady, gentle traction in latero-cranial direction to attain a reduction of tissue tension.
- **MYOFASCIAL RELEASE TO THE THORACIC INLET** – The operator's hands are placed with the thumbs lying posteriorly over the transvers processes of T1 and the fingers anteriorly over the clavicles and the first two ribs. First the direction of greatest freedom is determined and restrictions are tried to be released using an indirect technique (maintaining direction of ease). As a second step, a direct technique may be used (taking the tissue towards the direction of bind) until a release is palpated. The direct technique is only conducted if tissue restrictions are still palpable after applying the indirect technique.

Table 3: *Summary of standardized osteopathic manipulative treatment (OMT) techniques applied in the management of pneumonia in the OMT-study and their expected effects according to literature (Kline, 1965; Noll et al., 2010; Watson & Percival, 1939).*

OMT TECHNIQUE	EXPECTED EFFECT
❖ **Soft Tissue of Cervical, Thoracic and Thoracolumbar Area**	Cervical: ➢ relaxes secondary muscles of respiration ➢ improves sympathetic and parasympathetic nerve flow trough neck musculature Thoracic / Thoracolumbar: ➢ relaxes thoracic paraspinal muscles ➢ aids breathing ➢ increases motion of the rib cage ➢ reduces pulmonary congestion and sustains heart action
❖ **Rib Raising**	➢ Improves movement of the ribs and thoracic cage ➢ Mechanically stimulates the sympathetic chain ganglia and related structures → improved sympathetic tone in the lungs
❖ **Doming the Diaphragm**	➢ Improves motion of diaphragm ➢ Releases connective tissue tension within structures of the thorax
❖ **Suboccipital Decompression**	➢ Improves parasympathetic function ➢ Releases restricted tissues around vagal nerves
❖ **Myofascial Release to the Thoracic Inlet**	➢ Releases tissue restriction ➢ Promotes lymphatic drainage ➢ Improves pulmonary function and lymphatic circulation
❖ **Light Stroking to the Lower Intercostal Spaces**	➢ Promotes lymphatic drainage ➢ Augments lymphatic fluid circulation ➢ Relaxes muscles of respiration

❖ **LIGHT STROKING TO THE LOWER INTERCOSTAL SPACES AS A LYMPHATIC TECHNIQUE** – The operator softly places her fingers in the intercostal spaces of the lower ribs close to the costothoracic joints. Starting there, the operator softly strokes along the intercostal

spaces from dorsomedial towards anterolateral. Light pumping motion with the operator's fingertips using the operator's arms as a lever and the contact-area of the operator's elbows as a fulcrum can be performed in areas where congestion is palpated. The technique is repeated 3 to 5 times.

These six standardized techniques are designed to relax the patient, release restricted ribs and musculoskeletal issues that could increase or cause pathologic sympathetic and parasympathetic responses to the patient's disease and to enhance the patient's circulatory and lymphatic flow (Noll et al., 2008).

Not-standardized techniques are not strictly recorded in the study's forms but are allowed to use in case of finding SDF unique for this patient.

4.6. SAMPLE SIZE

According to Issac and Michael (1995) a pilot study sample should be 10 to 30 participants whereas Julious (2005) recommends 12 participants per group in the medical field. Others (Connelly, 2008; Treece & Treece, 1982) advocate a pilot study sample size of 10% of the sample projected in the larger parent study. Nevertheless, Hertzog (2008) points out that these studies are influenced by so many factors, that it is not a straight forward issue to resolve. Considering the fact that the present study includes different pre-defined subgroups and for this the sample size has to be large enough to be split in 4 groups, a minimum of 20 participants per main group was chosen to be accurate.

4.7. STATISTICAL ANALYSIS

Descriptive statistics are presented in Tables 4 to 10.

To analyse normal distribution of values, the Shapiro-Wilk test was conducted and histograms with normality curves were created as an additional visual test.

Categorical baseline data were analysed by Chi-square tests to detect significant differences in the distribution between intervention and control group. Numeric baseline characteristics were analysed by independent samples t-tests with a 95% confidence interval (CI).

Independent samples t-tests were also conducted to determine significant differences in mean and standard deviation of the primary outcome measures (LOS, DOF, DOT, SatO2) between the two groups and to analyse numeric secondary outcome measures (duration of total, PO and IV antibiotics) regardless of normal or non-normal distribution of values. According to Bortz and Döring (2010) the complementation of t-tests typically requires a normally distributed population but different Monte Carlo Studies already proved the robustness of these tests to such violations by providing statistically reliable results (cf. Bonneau, 1960; Glass, Peckham, & Sanders, 1972; Sawilowsky & Blair, 1992). Furthermore, t-tests show a stronger power than

non-parametric tests (such as Mann-Whitney-U-test) and are therefore to be favoured. Categorical secondary outcome measures (mortality, number of nosocomial infection and diagnosis of CLD) were analysed by Chi-square tests.

Furthermore, each primary outcome measure is independently analysed in each of the four predefined study subgroups. Therefore, a non parametric test (Kruskal-Wallis-Test) was carried out with the primary outcome measure as dependent variable and the subgroup as factor.

The study is analysed on an intention-to-treat (ITT) basis. A set p-value of 0.05 was considered significant, excepting the Kruskal-Wallis-Test where Bonferroni's correction was applied. All statistical analyses were completed using SPSS 24 statistics software.

5. RESULTS

A total of 50 patients hospitalized with pneumonia at Angkor Hospital for Children were screened for eligibility for a study conducted from January to March 2016. Two patients were older than five years of age and therefore did not meet the inclusion criteria. One patient's caretaker declined participation of her child and two children were discharged home before being enrolled by the co-researchers. 45 subjects were randomized but four patients withdrew from the study after enrolling. One of these patients dropped out because of a change in diagnosis - from pneumonia to asthma, and one was excluded because the research team later found out that the child was hospitalized within the last 14 days at a different hospital. Two patients were discharged from the hospital without a complete cure of pneumonia and therefore excluded from data analyses. One of them was discharged for palliative care due to a grade IV ventricular haemorrhage and the other was discharged and referred to a different hospital on parental request.

41 eligible patients completed the study protocol and were randomly placed into two groups: 20 in the intervention group and 21 in the control group. (s. Figure 4)

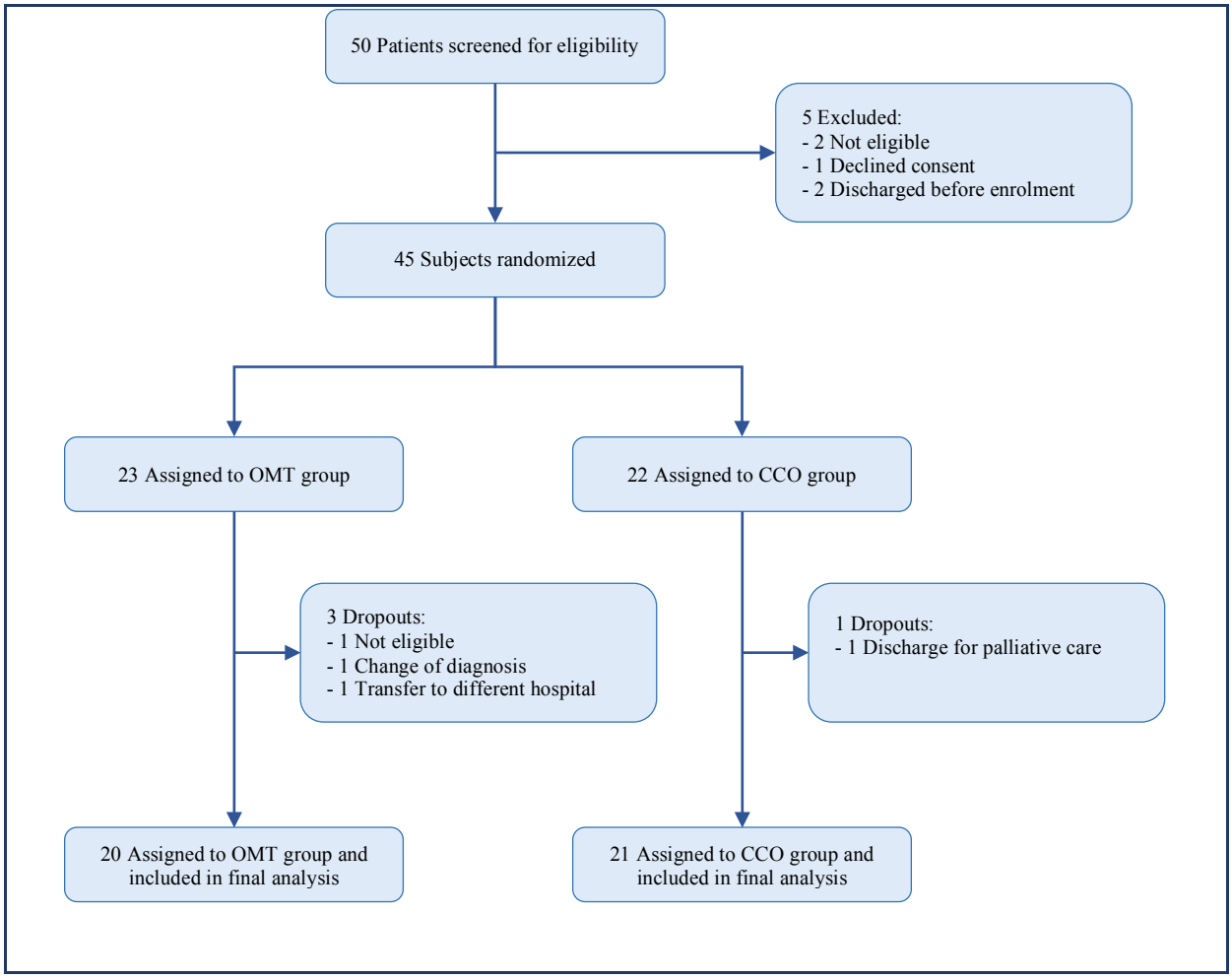

Figure 4: *Flow diagram of the Osteopathy study in Children with Pneumonia. OMT = osteopathic manipulative treatment / intervention group; CCO = conventional care only / control group*

5.1. TESTING NORMAL DISTRIBUTION

The value distribution of primary and secondary measures of both groups were analysed using the Shapiro-Wilk test (s. APPENDIX D). Due to the small sample size no normal distribution could be found and thus additional histograms were constructed for a visual test in order to see if the values might be nearly normally distributed. Most numeric values of the outcome measures, especially of the CCO group, are not normally distributed and thus need to be treated with caution. Only the values of duration of fever in both groups can be interpreted as nearly normally distributed according to visual analyses. The values as well as the normal curve of primary outcome measures (LOS, DOT, DOF and SatO2) of both groups are presented in Figure 5 and Figure 6. Figure 7 shows the value distribution as well as the respective normal curve of the secondary outcome "duration of antibiotics intake (total, IV and PO)" of the intervention and control group.

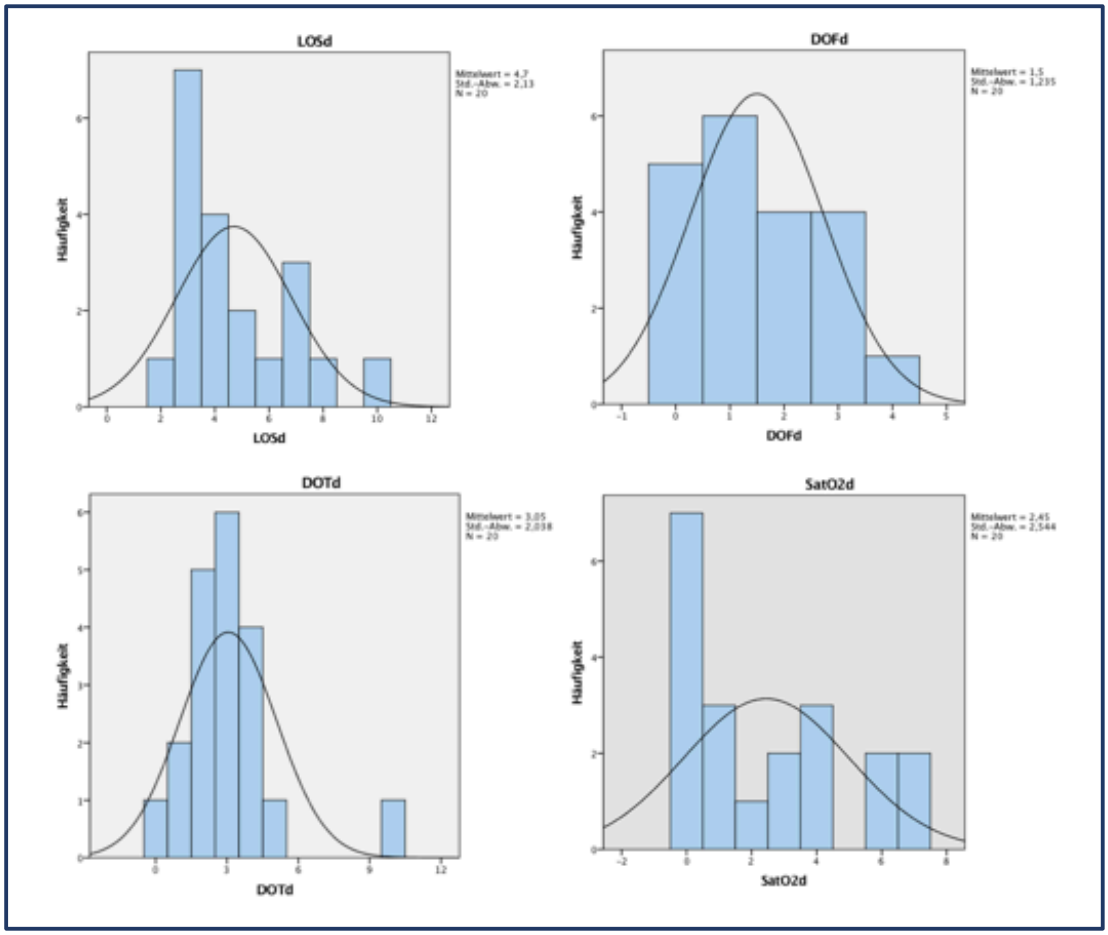

Figure 5: Histograms and normal curves of primary measures (LOT, DOF, DOT and SatO2) of the OMT group.

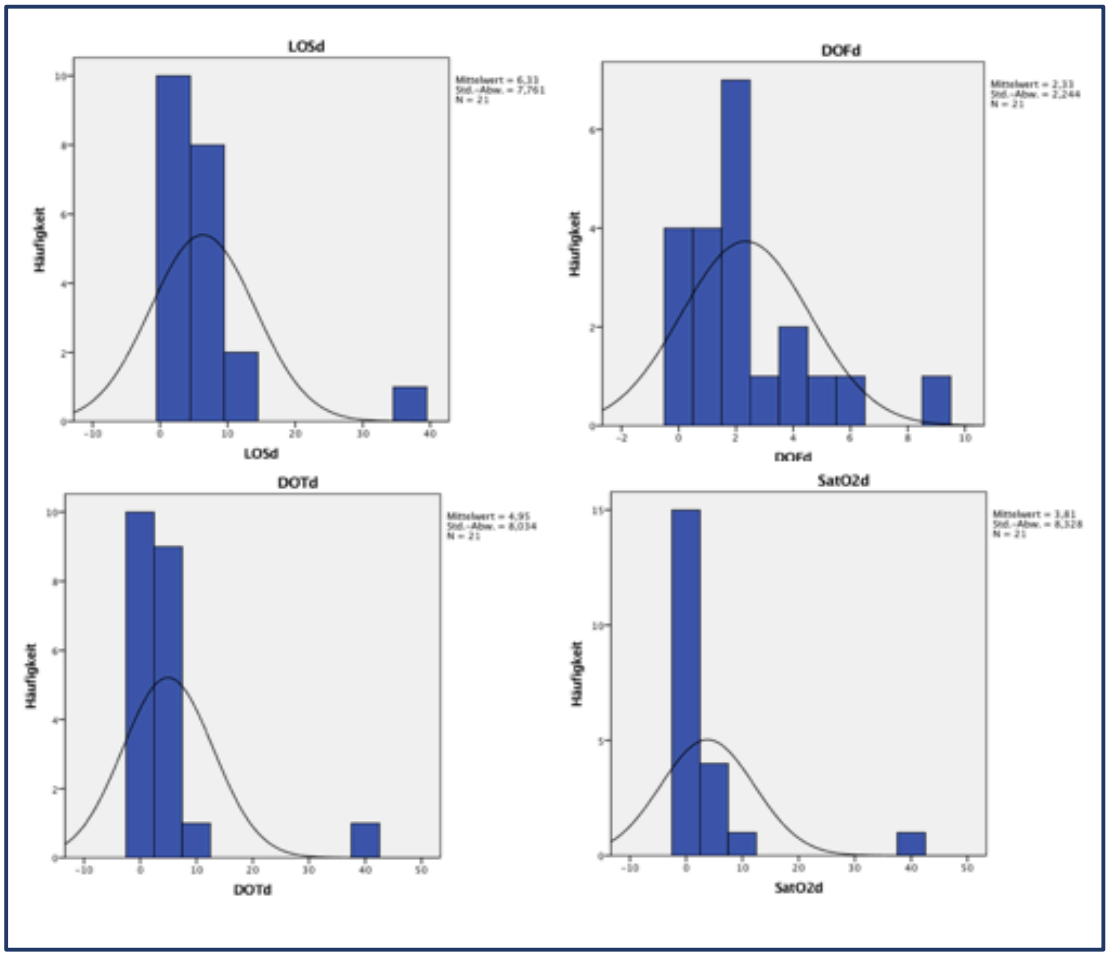

Figure 6: Histograms and normal curves of primary measures (LOS, DOF, DOT and SatO2) of the CCO group.

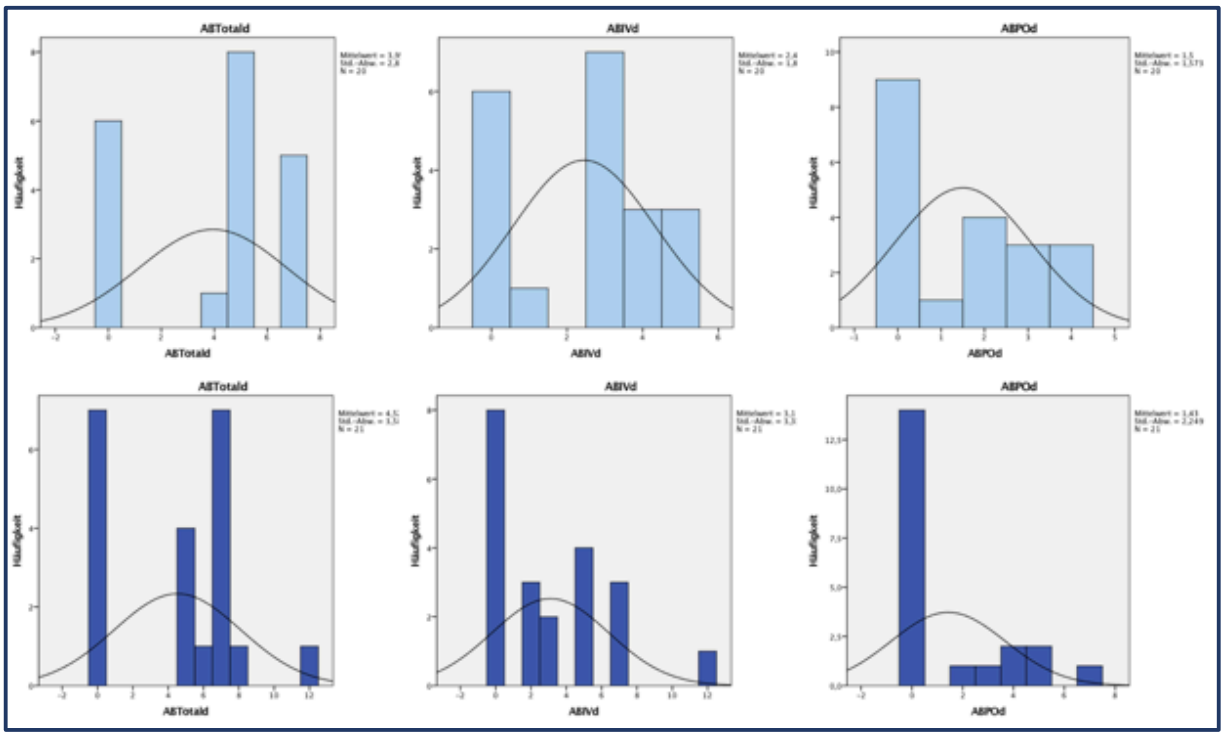

Figure 7: Histograms and normal curves of secondary outcome "duration of antibiotics intake" (total, IV and PO) of the OMT group (light blue) and CCO group (dark blue).

5.2. BASELINE CHARACTERISTICS OF PARTICIPANTS

In the following, the sample composition of the sample of N=41 shall be further examined. Three times more boys (n=31) than girls (n=10) were enrolled in the study. Participants had a mean age (SD, CI) of 0.8 (0.5, 1.1) years; 0.67 (0.43, 0.92) years in the OMT and 0.96 (0.65, 1.25) years in the CCO group. 16 patients were admitted to Intensive Care Unit (ICU); 9 patients (45%) in OMT group and 7 patients (33.3%) in CCO group. Each group had 2 participants who were born with low body weight (< 2000g) and 1 patient with history of tuberculosis in the family. 1 patient in OMT group and 2 patients in CCO group were premature and 2 patients in the intervention group were suffering from malnutrition while no patient in the control group was. Furthermore, the OMT group had double the number of patients who were additionally suffering from chronic diseases (OMT: n=6; CCO: n=3) including but not limited to chronic heart disease (CHD), HIV, cerebral palsy (CP) and chronic lung disease (CLD). A chi-square test did not show any significant difference (p=0.65) between the OMT and the CCO group. No mother was smoking.

Chi-square tests as well as independent samples t-tests were conducted to analyse all the baseline data of study participants in order to see if there are any significant differences. No significant differences between the two groups were found regarding general characteristics such as age, gender, low birth weight, prematurity, maternal smoking, history of tuberculosis in the family, ICU admission, malnutrition and chronic illnesses. All 41 patients were admitted with cough and chest indrawings. Respiratory symptoms and signs were similar between OMT and CCO groups concerning fever, respiratory rate and arterial oxygen saturation. The mean fever on the day of admission was 37.1 (0.8, 37.5) °C in the OMT group and 37.6 (0.9, 38.0) °C in the CCO group (p=0.23). Mean respiratory rate was 57.8 (9.3, 62.2) breaths per minute (bpm) (OMT: 59.9 [10.2, 64.7] bpm; CCO: 55.8 [8.4, 59.6] bpm) and the mean arterial oxygen saturation was 95.9% (4.6, 98.0%); 95.6% (4.5, 97.7%) in OMT group and 96.1% (4.7, 98.2%) in CCO group. A significant difference between the groups was found in auscultation: fine crackles were auscultated at 4 participants of the OMT group and at 12 participants of the CCO group (p=0.02) whereas coarse crackles were auscultated at 15 patients of the OMT group and at 9 patients of the CCO group (p=0.04).

Statistical analysis of chest radiographic findings did not show any significant differences. In fact, the value distribution was almost even in both groups with one minor exception of cardiac failure. More than twice the amount of cardiac failure was diagnosed on patients in the OMT group (n=5) compared to the CCO group (n=2). 8 patients in the OMT group and 10 patients in the CCO group presented consolidation on chest X-rays. Both groups included 1 patient with atelectasis and no patients with pleural effusion or tuberculosis. 2 patients in OMT group and 3 patients in CCO group were radiological diagnosed with hyper inflated lungs. Another 2 patients in each group showed other radiographic findings (such as bronchial wall thickening) as well as 5 patients in OMT group and 7 patients in CCO group did not show any findings on

their chest X-rays. A summary of the baseline characteristics and their p-values is provided in the following Table 4.

Table 4: *Baseline Characteristics of Study Subjects (N=41)*

BASELINE CHARACTERISTICS	GROUP		P VALUE
General information	**OMT (n=20)**	**CCO (n=21)**	
Mean age in years (SD, CI)	0.67 (0.43, 0.92)	0.96 (0.65, 1.25)	0.07**
Gender			0.52*
Female	4 (20.0%)	6 (28.6%)	
Male	16 (80.0%)	15 (71.4%)	
Low birth weight (<2000g)	2 (10.0%)	2 (9.5%)	0.96*
Premature	1 (5.0%)	2 (9.5%)	0.58*
Maternal smoking	0 (0.0%)	0 (0.0%)	
History of tuberculosis in the family	1 (5.0%)	1 (4.8%)	
Admitted to ICU	9 (45.0%)	7 (33.3%)	0.44*
Malnutrition	2 (10.0%)	0 (0.0%)	0.14*
Chronic illnesses (included but not limited to CHD, HIV, CP, CLD)	6 (30.0%)	3 (14.3%)	0.65*
Respiratory symptoms and signs			
Coughing	20 (100%)	21 (100%)	
Mean fever in °C (SD, CI)	37.1 (0.8, 37.5)	37.6 (0.9, 38.0)	0.23
Mean respiratory rate in bpm* (SD, CI)	59.9 (10.2, 64.7)	55.7 (8.4, 59.6)	0.91
Mean arterial oxygen saturation in % (SD, CI)	95.6 (4.5, 97.7)	96.1 (4.7, 98.2)	0.35
Chest in-drawings	20 (100%)	21 (100%)	
Auscultation:			

Fine crackles	4 (20.0%)	12 (57.1%)	0.02
Coarse crackles	15 (75.0%)	9 (42.9%)	0.04
Wheezes	11 (55.0%)	8 (38.1%)	0.28
Chest radiographic findings			
Consolidation	8 (40.0%)	10 (47.6%)	0.62
Atelectasis	1 (5.0%)	1 (4.8%)	0.97
Hyperinflation	2 (10.0%)	3 (14.3%)	0.68
Pleural effusion	0 (0.0%)	0 (0.0%)	
Tuberculosis	0 (0.0%)	0 (0.0%)	
Cardiac failure	5 (25.0%)	2 (9.5%)	0.19
Others	2 (10.0%)	2 (9.5%)	0.96
Non	5 (25.0%)	6 (28.6%)	0.80

**Bpm=breaths per minute*

5.3. OUTLIERS

Outcomes of clinical studies are clearly affected by extreme values of certain patients, which was the case in this research as well. As mentioned before, one patient of the control group diagnosed with pneumonia died on day 38 due to respiratory failure. His condition was very severe from day one on until death. Most of the recorded values of this specific patient are extremely high compared to others and therefore have to be classified as outliers. Furthermore, Figure 8 shows a second outlier in the CCO group, whereas no comparable patient was found in the OMT group (Figure 9). Outliers in this study were chosen not to be dropped because they are good examples for the severity and acuteness of pneumonia. According to that, results will thus be critically analysed and possible effects of the outliers will be included in the final discussion.

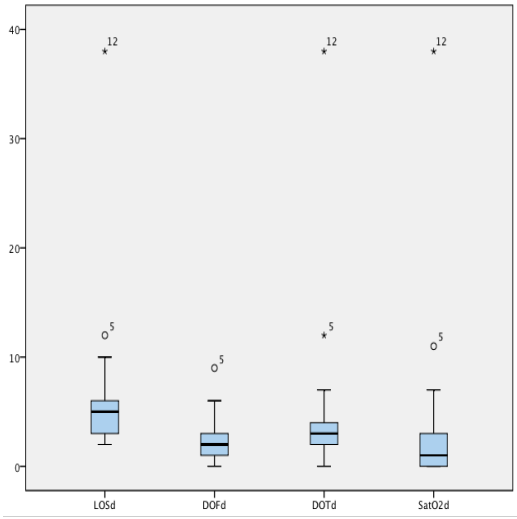

Figure 8: Boxplot of the primary outcome measures of the CCO group.

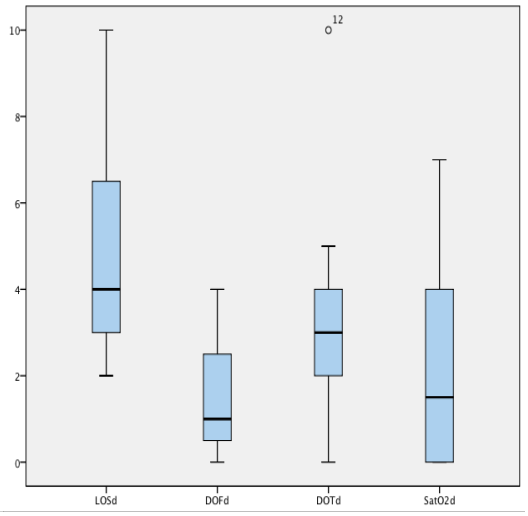

Figure 9: Boxplot of the primary outcome measures of the OMT group.

5.4. PRIMARY OUTCOME MEASURES

Independent samples t-tests were conducted to analyse the values of length of hospital stay (LOS), duration of fever (DOF), duration of tachypnea (DOT) and time until oxygen saturation was >90% (SatO2) between the OMT and the CCO group. For a better display of the impact of outliers, the median was calculated for each outcome in each group additionally. The statistical analysis showed no significant difference of any primary outcome measure between the two groups but did show a trend towards a reduction of LOS, DOF and SatO2 comparing the mean and median values of each group. A summary of the mean and median values per group including the p-values is shown in **Table 5** and for a better comparison, the mean values are as well presented in a bar chart in Figure 10.

Table 5: *Summary of primary outcome measures of study subjects.*

PRIMARY OUTCOME MEASURES		GROUP		P VALUE
mean (SD, 95%CI)		**OMT (n=20)**	**CCO (n=21)**	
LOS in days	mean (SD, 95%CI)	4.7 (2.1, 5.7)	6.3 (7.8, 9.9)	0.19
	median	4	5	
DOF in days	mean (SD, 95%CI)	1.5 (1.2, 2.1)	2.3 (2.2, 3.4)	0.08
	median	1	2	
DOT in days	mean (SD, 95%CI)	3.1 (2.0, 4.0)	5.0 (8.0, 8.6)	0.16
	median	3	3	
SatO2 in days	mean (SD, 95%CI)	2.5 (2.5, 3.6)	3.8 (8.3, 7.6)	0.24
	median	0	1	

The LOS of subjects in the OMT group showed a mean of 4.7 (2.1, 5.7) days compared to a mean of 6.3 (7.8, 9.9) days in the CCO group, analysed on ITT basis (p=0.19). Comparing the total DOF of both groups, the intervention group shows a lower mean value of 1.5 (1.2, 2.1) days, whereas a mean of 2.3 (2.2, 3.4) days could be found in the control group (p=0.08). Subjects of the OMT group had a mean of 3.1 (2.0, 4.0) days in total DOT, while the mean of subjects of the CCO group was 5.0 (8.0, 8.6) days regarding DOT (p=0.16). The mean duration until patients' arterial oxygen saturation was >90% was 2.5 (2.5, 3.6) days in OMT group compared to 3.8 (8.3, 7.6) days in CCO group (p=0.24). In summary, the lower mean values of LOS, DOF, DOT and SatO2 showed a trend in favour of the OMT group.

The median of the LOS was 4 days in the OMT group compared to 5 days in the CCO group. The median of the duration of fever was also one day shorter in the intervention than in the control group (OMT=1 day, CCO=2 days), while the median of the DOT was the same in each of the groups (3 days). The mean duration until oxygen saturation was >90% also showed a trend towards a reduction in the OMT (0 days) compared to the CCO group (1 day).

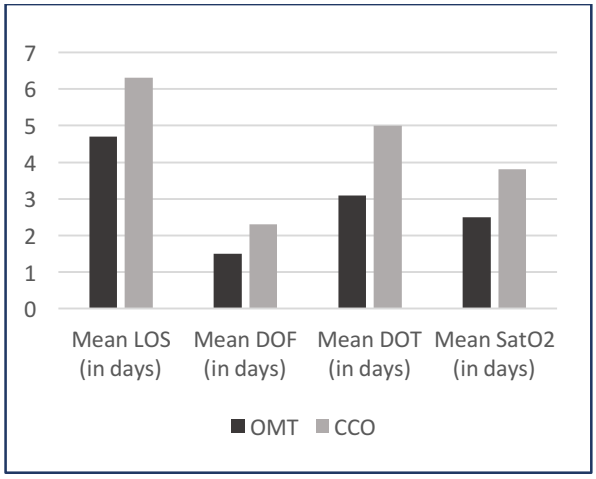

Figure 10: Mean values of primary outcome measures comparing OMT group vs. CCO group.

5.5. SECONDARY OUTCOME MEASURES

Chi-square tests were conducted to analyse the categorical values of secondary outcomes, such as mortality, nosocomial infection (NCI) and chronic lung disease (CLD) at discharge. One subject of the CCO group died during the study and no patient died in the OMT group. That difference is nonsignificant (p=0.32). The 3 months old male patient of the CCO group died on day 38 of hospital stay on intensive care unit, after three failed attempts of extubation. Cause of death was investigated by AHC's medical staff according to the hospital's standards and respiratory failure due to nosocomial infection was determined.

The statistical analysis revealed a significant difference between the two groups regarding nosocomial infection (p=0.04) with no NCI in the OMT group and 4 nosocomial infections in the CCO group. The values of CLD at discharge did not show any statistical significance comparing both groups (p=0.55; OMT=1, CCO=2). Independent samples t-tests were used to compare the mean values of the duration of total, intravenous and oral antibiotics intake in the intervention and the control group. The tests did not show any statistical difference regarding antibiotics intake between the two groups. The mean duration of total antibiotics intake was 3.9 (2.8, 5.3) days in the OMT group, while the mean duration in the CCO group was 4.5 (3.6, 6.2) days. The median of total intake of antibiotics was 5 days in both groups. The duration of IV antibiotics showed a mean of 2.5 (1.9, 3.3) days in the intervention and a mean of 3.1 (3.3, 4.6) days in the control group. Furthermore, the OMT group had a mean of 1.5 (1.3, 2.19) days and the CCO group 1.4 (2.3, 2.43) days in duration of PO antibiotic intake. In contrast, the median shows a higher value in IV antibiotics intake as well as PO antibiotics intake for the OMT group (IV=3 days, PO=2 days) than the CCO group (IV=2 days, PO=0 days). A bar chart in Figure 11 presents a summary, comparing the mean values while the boxplot in Figure 12. shows the median values of antibiotics intake (total, IV, PO) of both groups. Table 6 summarizes the incidences and mean values per group as well as the p-values of the secondary outcome measures.

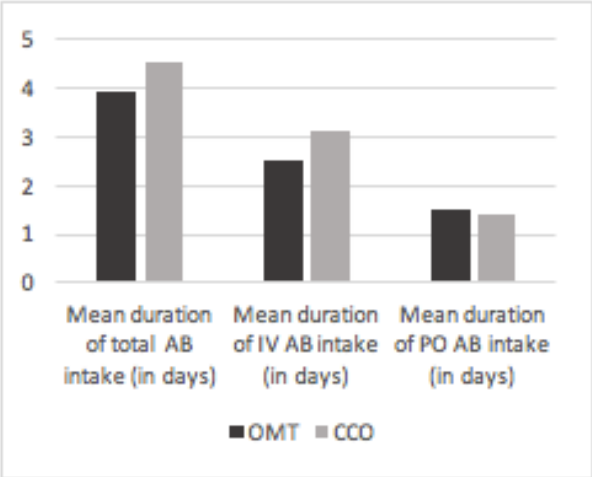

Figure 11: Bar chart of mean duration of antibiotics intake (total, IV, PO) comparing the OMT with the CCO group.

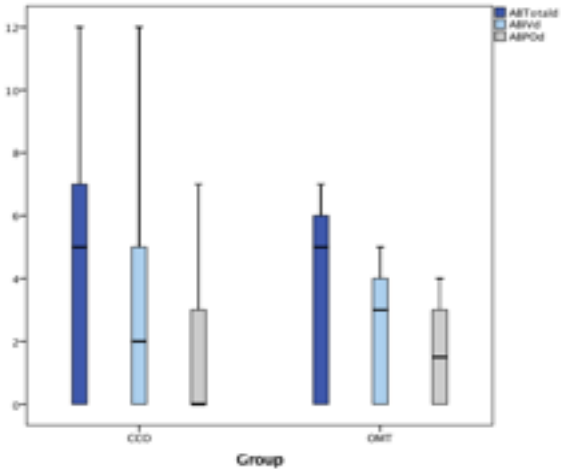

Figure 12: Boxplot of median duration of antibiotics intake (total, IV, PO) comparing the OMT and the CCO group

Table 6: Summary of secondary outcome measures of study subjects.

SECONDARY OUTCOME MEASURES	GROUP		P VALUE
	OMT (n=20)	CCO (n=21)	
Mortality	0	1	0.32
Nosocomial infection	0	4	0.04
Mean and median duration of antibiotic intake (IV and PO) in days	3.9 (2.8, 5.3)* 5.0**	4.5 (3.6, 6.2)* 5.0**	0.57
Mean and median duration of IV antibiotics in days	2.5 (1.9, 3.3) 3.0**	3.1 (3.3, 4.6)* 2.0**	0.23
Mean and median duration of PO antibiotics in days	1.5 (1.3, 2.19)* 1.5**	1.4 (2.3, 2.43)* 0.0**	0.09
CLD at discharge	1	2	0.55

** Mean (SD, 95% CI); ** median*

5.6. PRE-DEFINED STUDY SUBGROUPS

The values of the pre-defined study subgroups appeared to be not normally distributed. Therefore, a non-parametric test (Kruskal-Wallis test) was carried out with the respective primary outcome measure as dependent variable and the subgroups as factor to analyse each primary outcome separately in each of the four pre-defined subgroups. Bonferroni's correction was applied whenever the p-value was significant. Consequently, Bonferroni corrected p-values were stated in particular cases. In the pre-defined subgroup IV "Chronic lung disease & no chronic lung disease" the sample size of the group of children suffering from a CLD was too small to perform a Kruskal-Wallis test and therefore an independent samples t-test (Bortz & Döring, 2010) was conducted only for the other group, children not suffering from a CLD.

I. RADIOGRAPHIC PNEUMONIA & WHO-DEFINED CLINICAL PNEUMONIA ONLY

The value distribution in the radiographic pneumonia and the WHO-defined clinical pneumonia only group was almost identical. 11 children in the OMT group and 12 children in the CCO group were diagnosed with radiographic pneumonia. Each of the groups included 9 patients with WHO-defined pneumonia only. ITT statistical analyses found no significant differences for any primary outcome measure comparing the two groups. A summary of mean values, median values, p-values and Bonferroni-corrected p-values are presented in **Table 7**.

Table 7: Radiographic pneumonia and WHO-defined clinical pneumonia only: summary of mean values and p-values of OMT and CCO groups

		RADIOGRAPHIC PNEUMONIA		WHO-DEFINED CLINICAL PNEUMONIA ONLY		P VALUE	B. CORR
		OMT (n=11)	CCO (n=12)	OMT (n=9)	CCO (n=9)		
LOS in days	Mean (SD, CI)	4.2 (1.3, 5.1)	8.6 (9.8, 14.8)	5.3 (2.8, 7.5)	3.3 (1.3, 4.4)		
	Median	4	5.5	5	3	0.11	
DOF in days	Mean (SD, CI)	1.6 (1.2, 2.4)	3.2 (2.6, 4.8)	1.4 (1.3, 2.5)	1.2 (0.8, 1.9)		
	Median	1	2.5	1	1	0.17	
DOT in days	Mean (SD, CI)	3.1 (1.4, 4.0)	7.3 (10.2, 13.7)	3.0 (2.7, 5.1)	1.9 (1.2, 2.8)		
	Median	3	3.5	2	2	0.04	1.00* 1.00**
SatO2 in days	Mean (SD, CI)	2.0 (3.3, 3.5)	6.1 (10.6, 12.8)	3.0 (2.9, 5.2)	0.8 (0.8, 1.4)		
	Median	1	2.5	3	1	0.25	

** p_{BON} of radiographic pneumonia group; ** p_{BON} of WHO-defined clinical pneumonia group*

- Mean (SD, 95% CI) and median of subjects with radiographic pneumonia:

The LOS showed a trend towards a reduction in the OMT group with a mean of 4.2 (1.3, 5.1) days compared to a twice as high mean of 8.6 (9.8, 14.8) days in the CCO group and a median of 4 days in the OMT versus 5.5 days in the CCO group. A similar tendency appeared for the DOF. The OMT group had a mean of 1.6 (1.2, 2.4) days and a median of 1 day, whereas the CCO group had a mean of 3.2 (2.6, 4.8) days and a median of 2.5 days. Furthermore, the mean value of DOT was lower in the intervention group (3.1 [1.4, 40] days) compared to that of the control group (7.3 [10.2, 13.7] days), while the median values in those groups were similar with 3 days in the OMT group versus 3.5 days in the CCO group. The duration until oxygen saturation was >90% had a mean of 2.0 (3.3, 3.5) days and a median of 1 day in the OMT group. A three times greater mean of 6.1 (10.6, 12.8) days and a median of 2.5 days could be found in the CCO group.

- Mean (SD, 95% CI) and median of subjects with WHO-defined clinical pneumonia only:

In contrast to the previous findings, the LOS of patients with WHO-defined clinical pneumonia had a mean of 5.3 (2.8, 7.5) days and a median of 5 days in the OMT group and were therefore higher than those in the CCO group with a mean of 3.3 (1.3, 4.4) days and a median of 3 days. Comparing the DOF in both groups showed almost equal results with a mean of 1.4 (1.3, 2.5) days in the OMT group and 1.2 (0.8, 1.9) days in the CCO group and median values of 1 day in both groups. The mean DOT was one day longer in the OMT group (3.0 [2.7, 5.1] days) than in the CCO group (1.9 [1.2, 2.8] days) and identical comparing their median values (1 day). Showing the opposite result to that of the radiographic pneumonia group, the duration until oxygen saturation was >90% was three times longer in the intervention group (mean: 3.0 [2.9, 5.2] days, median: 3 days) than in the control group (mean: 0.8 [0.8, 1.4] days, median: 1 day).

II. VENTILATION SUPPORT & NO VENTILATION SUPPORT

8 children assigned to the OMT group and 5 children assigned to the CCO group were in need of ventilation support (invasive support and/or CPAP) whereas 12 patients in the OMT and 16 patients in the CCO group were not in need of any ventilation support. A summary of mean values, median values, p-values and Bonferroni-corrected p-values are presented in **Table 8**.

- Mean (SD, 95% CI) and median of subjects with ventilation support:

ITT analysis found no significant difference between the groups of children with ventilation support regarding LOS, DOF and DOT and SatO2 after Bonferroni's correction, where a p-value of 0.05 or less was considered to be significant.

The mean LOS was 6.9 (1.6, 8.2) days in the OMT group and therefore half of the mean LOS in the CCO group with 14.8 (13.1, 31.1) days. The median of LOS was 7 days in OMT group and 10 days in the CCO group (p_{BON}=1.00). In addition, the mean DOF showed a trend towards a reduction in favour of the intervention group (OMT: mean 2.4 [1.2, 3.4] days, median 2.5 days; CCO: mean 5.2 [2.4, 8.2] days, median 4 days; p_{BON}=0.67). The mean DOT showed a three times smaller value in the OMT group (4.1 [2.6, 6.3] days) than in the CCO group (12.8 [14.5, 30.8] days). The median of DOT in the OMT group (3.5 days) is half of that of the CCO group (7 days) (p_{BON}=1.00). The difference was non-significant due to the small sample size. The duration until oxygen saturation was >90% showed a mean of 5.1 (1.6, 6.4) days and a median of 5 days in the OMT group versus a mean of 12.6 (14.6, 30.8) days and a median of 7 days in the CCO group (p_{BON}=1.00). Remarkable is the fact that the mean of the CCO group was more than twice as high as that of the OMT group.

- Mean (SD, 95%CI) and median of subjects without ventilation support:

The mean values of the OMT and the CCO group of children without ventilation support were almost identical. The mean LOS was 3.3 (0.6, 3.6) days in the OMT group and 3.7 (1.7, 4.6) days in the CCO group. The median was 3 days in each of the groups (p_{BON}=1.00). DOF showed a mean value of 0.9 (0.9, 1.5) days in the OMT group and 1.4 (1.3, 2.1) days in the CCO group (median: OMT=1 day; CCO=1.5 days; p_{BON}=1.00). DOT showed a mean of 2.3 (1.2, 3.1) days and a median of 2.5 days in the OMT group versus a mean of 2.5 (1.7, 3.4) days and a median of 2 days in the CCO group (p_{BON}=1.00). The mean duration until oxygen saturation was >90% was 0.7 (1.0, 1.3) days (median=0 days) in the OMT and 1.1 (1.2, 1.7) days (median=1 day) in the CCO group (p_{BON}=1.00).

Table 8: *Ventilation support & no ventilation support: summary of mean values, p-values and Bonferroni-corrected p-values between OMT group and CCO group.*

		VENTILATION SUPPORT		NO VENTILATION SUPPORT		P VALUE	B. CORR.
		OMT (n=8)	CCO (n=5)	OMT (n=12)	CCO (n=16)		
LOS (d)	Mean (SD, CI)	6.9 (1.6, 8.2)	14.8 (13.1, 31.1)	3.3 (0.6, 3.6)	3.7 (1.7, 4.6)		
	Median	7	10	3	3	<0.01	1.00* 1.00**
DOF (d)	Mean (SD, CI)	2.4 (1.2, 3.4)	5.2 (2.4, 8.2)	0.9 (0.9, 1.5)	1.4 (1.3, 2.1)		
	Median	2.5	4	1	1.5	<0.01	0.67* 1.00**
DOT (d)	Mean (SD, CI)	4.1 (2.6, 6.3)	12.8 (14.5, 30.8)	2.3 (1.2, 3.1)	2.5 (1.7, 3.4)		
	Median	3.5	7	2.5	2	<0.01	1.00* 1.00**
SatO2 (d)	Mean (SD, CI)	5.1 (1.6, 6.4)	12.6 (14.6, 30.8)	0.7 (1.0, 1.3)	1.1 (1.2, 1.7)		
	Median	5	7	0	1	<0.01	1.00* 1.00**

** p_{BON} of ventilation support group; **p_{BON} of no ventilation support group*

III. CHRONIC HEART DISEASE & NO CHRONIC HEART DISEASE

6 children eligible for data analysis were diagnosed with chronic heart disease. 4 of these children were randomly assigned to the OMT group and 2 were randomly assigned to the CCO group. The remaining children, 16 in the OMT group and 19 in the CCO group, did not suffer from any chronic heart disease. ITT analyses did not show any significant differences between any of the subgroups. **Table 9** presents a summary of mean values, median values and p-values of both groups.

***Table 9**: Chronic heart disease & no chronic heart disease: summary of mean values and median values*

		CHRONIC HEART DISEASE		NO CHRONIC HEART DISEASE		P VALUE
		OMT (n=4)	CCO (n=2)	OMT (n=16)	CCO (n=19)	
LOS (d)	Mean (SD, CI)	6.5 (2.7, 10.7)	7.0 (7.1, 70.5)	4.3 (1.8, 5.2)	6.3 (8.0, 10.1)	
	Median	6	7	3.5	5	0.48
DOF (d)	Mean (SD, CI)	2.0 (1.4, 4.3)	5.0 (5.7, 55.8)	1.4 (1.2, 2.0)	2.1 (1.7, 2.9)	
	Median	2.5	5	1	2	0.50
DOT (d)	Mean (SD, CI)	4.5 (3.8, 10.5)	6.5 (7.8, 76.4)	2.7 (1.3, 3.4)	4.8 (8.3, 8.8)	
	Median	3	6.5	3	3	0.94
SatO2 (d)	Mean (SD, CI)	4.0 (3.2, 9.0)	5.5 (7.8, 75.4)	2.1 (2.3, 3.3)	3.6 (8.6, 7.8)	
	Median	4.5	5.5	1.5	1	0.71

- Mean (SD, 95%CI) and median of subjects with chronic heart disease:

It should be avoided to conduct statistical analysis with a total sample size of 6 subjects. Still, a short summary of the values in **Table 9**: Chronic heart disease & no chronic heart disease: summary of mean values and median valuesis presented in the following section but must nevertheless be treated with caution.

The LOS was almost identical comparing both groups with a mean of 6.5 (2.7, 10.7) days / median of 6 days in the OMT and a mean and median of 7.0 (7.1, 70.5) days in the CCO group. The differences of mean and median values of DOF between the OMT group (mean: 2.0 [1.4, 4.3], median: 2.5 days) and the CCO group (mean: 5.0 [5.7, 55.8], median: 5 days) have to be critically assessed and might have been caused due to the small sample size. The same applies to the mean of DOT which also showed a reduction in favour of the OMT group (OMT: mean 4.5 [3.8, 10.5], median 3 days; CCO: mean and median of 6.5 [7.8, 76.4] days). The mean duration until oxygen saturation was >90% was 4.0 (3.2, 9.0) days (median: 4.5 days) in the OMT and 5.5 (7.8, 75.4) days (median: 5.5 days) in the CCO group.

- Mean (SD, 95%CI) and median of subjects without chronic heart disease:

In this group it is striking that there was a small trend in favour of the OMT group towards a reduction of mean values in all four primary outcomes but showing the opposite when the respective median values are compared. The LOS showed a mean of 4.3 (1.8, 5.2) days and a median of 3 days in the intervention group against a mean of 6.3 (8.0, 10.1) days and a median of 5 days in the control group. The DOF presented a mean value of 1.4 (1.2, 2.0) days and a median value of 1 day in the OMT group versus a mean of 2.1 (1.7, 2.9) days and a median of 2 days in the CCO group. The mean of DOT was 2.7 (1.3, 3.4) days in the OMT group and 4.8 (8.3, 8.8) days in the CCO group. The median of DOT was 3 days in both groups. The duration until oxygen saturation was >90% showed a mean of 2.1 (2.3, 3.3) days and a median of 1.5 days in the OMT group versus a mean of 3.6 (8.6, 7.8) days and a median of 1 day in the CCO group.

IV. CHRONIC LUNG DISEASE & NO CHRONIC LUNG DISEASE ON ADMISSION

3 subjects suffered from a chronic lung disease on admission and were randomly assigned into the two groups; one in the OMT group and two in the CCO group. Each group included 19 patients who did not suffer from any chronic lung disease on day of admission. The sample size in the group of children with a chronic lung disease was too small to be analysed. Patients with no chronic lung disease in the intervention and control groups were compared using an independent samples t-test (Bortz & Döring, 2010) with the primary outcome measures (LOS, DOF, DOT, SatO2) as test variable and the sub-group “no chronic lung disease” as group variable. ITT analyses did not find a significant difference in any of the primary outcome measures comparing children with no chronic lung disease in the OMT group to those in the CCO group. A summary of the mean values and p-values of both groups is presented in **Table 10**.

Table 10: *Chronic lung disease & no chronic lung disease: summary of mean values and p-values of OMT and CCO groups*

		CHRONIC LUNG DISEASE (ON ADMISSION)		NO CHRONIC LUNG DISEASE (ON ADMISSION)		P VALUE
		OMT (n=1)	CCO (n=2)	OMT (n=19)	CCO (n=19)	
LOS in days	Mean (SD, CI)	-	-	4.8 (2.2, 5.8)	6.5 (8.1, 10.4)	0.87*
	Median	-	-	4	5	
DOF in days	Mean (SD, CI)	-	-	1.5 (1.3, 2.1)	2.3 (2.6, 3.4)	0.69*
	Median	-	-	1	2	
DOT in days	Mean (SD, CI)	-	.	3.1 (2.1, 4.1)	5.1 (8.4, 9.1)	1.00*
	Median	-	-	3	3	
SatO2 in days	Mean (SD, CI)	-	-	2.5 (2.6, 3.8)	4.2 (8.7, 8.4)	0.41*
	Median	-	-	2	1	

** Independent sample t-test with primary outcome measure (LOS, DOF, DOT and SatO2) as testing variable and the sub-group "no chronic lung disease" as group variable.*

Comparing the two groups, a minor tendency towards a reduction of all mean values (SD, 95%CI) was found in favour of the OMT group with a mean LOS of 4.8 (2.2, 5.8) days in the OMT and 6.5 (8.1, 10.4) days in the CCO group (p=0.87), a mean DOF of 1.5 (1.3, 2.1) days in the OMT and 2.3 (2.6, 3.4) days in the CCO group (p=0,69), a mean DOT of 3.1 (2.1, 4.1) days in the OMT and 5.1 (8.4, 9.1) days in the CCO group (p=1.00) and a mean SatO2 of 2.5 (2.6, 3.8) days in the OMT and 4.2 (8.7, 8.4) days in the CCO group (p=0.41). Comparing the median values of both groups, the median of LOS was 4 days in the OMT group and 5 days in the CCO group. The median of DOF showed 1 day in the OMT versus 2 days in the CCO group. The median of DOT was equal in both groups with a duration of 3 days and the median of the time until oxygen saturation was >90% was 1 day longer in the OMT group (2 days) than in the CCO group (1 day).

6. DISCUSSION

The purpose of the present study was to evaluate the efficiency of OMT as an adjunctive treatment to conventional clinical care on children hospitalized with acute CAP in Cambodia. Hence, 41 eligible patients were randomly allocated to the OMT (n=20) and CCO (n=21) group and later analysed on an ITT basis. Data of 40 patients were analysed after discharge, whereas 1 patient's data were analysed after death. Although no statistically significant difference was found between any of the primary outcome measures such as hospital length of stay, duration of fever, duration of tachypnea and time until oxygen saturation was >90% comparing the intervention and the control group, the lower mean and median values of the OMT group work in favour of the Osteopathic Manipulative Treatment. Furthermore, a significant difference was found in one of the secondary outcomes, frequency of nosocomial infection (NCI). While no incidence of NCI occurred in the intervention group, 4 were found in the control group (p=0.04). Therefore, the NULL HYPOTHESIS: "there is no significant difference to be found in one or more of the measured primary and/or secondary outcomes comparing the intervention group (OMT) to the control group (CCO)" is to be rejected.

6.1. BASELINE CHARACTERISTICS

Although analysis of baseline data comparing the intervention to the control group did not show any significant differences, it was striking that three times more male (n=31) than female (n=10) subjects were recruited in the study. This finding correlates with a study of Jokinen et al. (1993) who also found a strong male incidence in children younger than 5 years of age (11.2/1000 males and 5.7/1000 in females).

6.2. PRIMARY OUTCOME MEASURES

The nonsignificant findings in this category stay in contrast to results of Noll et al.'s (2010) study on the effect of OMT on elderly patients with pneumonia (n=406), where PP analysis found a significant difference in the median of the length of hospital stay (3.5 days in OMT and 4.5 days in CCO group).

Kline's study (1965) from the sixties presented a mean LOS of 6.3 days in the OMT group, 5.8 days in the antibiotic group and 4.8 days in the OMT and antibiotic group with no significant difference. Although antibiotics – if needed – were part of standard care in the study at hand, outcomes between Kline's research and the present trial might be comparable. A similar tendency was found in this study's results using an independent samples t-test. It could be shown that there is a minor trend towards lower mean LOS in the intervention group (4.7 [2.1,5.7] days) compared to that of the control group (6.3 [7.8, 9.9]). This same trend was furthermore found in other primary outcomes such as duration of fever, duration of tachypnea and time until oxygen saturation was >90%. In contrast to that, the results have to be handled with particular caution due to outliers, not normally distributed values and a rather small sample size. Since

the median values are not affected by outliers (Bortz & Döring, 2010), a comparison of median values promises to carry more relevance than an analysis of mean values. Even though without a significant difference, the median values of hospital length of stay (OMT=4, CCO=5), duration of fever (OMT=1, CCO=2) and time until oxygen saturation is >90% (OMT=0, CCO=1) also resulted in favour of the intervention group.

6.3. SECONDARY OUTCOME MEASURES

Although nosocomial infections are a major health problem all over the world, no studies were found evaluating the effect of OMT on the frequency or recovery of these hospital acquired infections. Nosocomial infections cause a higher risk of mortality, an increased hospital length of stay (Fagon et al., 1993; Rosenthal et al., 2012) and last but not least an augmentation of medical care costs (Dixon, 1987). Therefore, methods to prevent NCI are particularly valuable, especially for hospital managements. The significant difference in frequency of nosocomial infection ($p=0.04$) in favour of the intervention group in this pilot study has the potential of being a new scientific discovery in the osteopathic field and opens an interesting and wide area of research.

No significant differences were found regarding mortality, duration of antibiotics intake and frequency of chronic lung disease at discharge. These findings are partly in contrast to the results of Noll et al (2010) who found a significantly lower median of the duration of intravenous antibiotics and treatment endpoint (death or respiratory failure) in the OMT group than in the CCO group. Looking at the results of this study, it is striking, that the mean and median values of intravenous and oral antibiotics do not show the same tendency. While the mean values are lower in the OMT group, the median values are higher in the OMT group compared to those of the CCO group. This might be a hint for a falsifying effect of the outliers on the results as well as the small sample size in general.

No previous studies concerning the frequency of chronic lung disease at discharge could be found and the outcome in this pilot study has to be ignored as well. None of the patients was newly diagnosed with a chronic lung disease because all patients were already presented with CLD on day of admission. Therefore, this secondary outcome is invalid.

6.4. PRE-DEFINED STUDY-SUBGROUPS

The main reason for creating the pre-defined subgroups was to determine differences in outcomes in the intervention and the control group when comparing smaller groups, which are likely to include patients with a different severity of pneumonia (radiographic pneumonia / WHO-defined clinical pneumonia only and ventilation support / no ventilation support) and to find a way to deal with severe, additional diagnoses, without excluding patients from this trial (chronic heart disease / no chronic heart disease and chronic lung disease / no chronic lung disease). The analysis did not find a statistical significance in any of the primary outcome measures comparing the intervention and the control group in any of the four subgroups. The

not normally distributed values in the different groups led to the conduction of a non-parametric test (Kruskal-Wallis test) and thus the median values were compared. In the following paragraphs, observable trends of the pre-defined subgroups are being discussed.

In the group of subjects with radiographic findings, the median values of hospital length of stay (OMT=4 days, CCO=5.5 days), duration of fever (OMT=1day, CCO=2.5days) and time until oxygen saturation was >90% (OMT=1 day, CCO=2.5days) resulted in favour of the OMT group compared to that of the CCO group. In contrast, the results of assumingly less severely sick children in the WHO-defined clinical pneumonia only group showed median values, which rather resulted in favour of the control group regarding hospital length of stay (OMT=5 days, CCO=3 days) and time until oxygen saturation was >90% OMT=3 days, CCO=1 day). Possible reasons for these results may lie in the design of OMT protocol and in the investigator's lack of experience with children. With most of the patients, therapy turned out to be more difficult the healthier and therefore more active the child was. Focusing on therapy while the patient was exceedingly mobile, proofed to be a challenge for the performing osteopath. As a result, these outcomes may have been slightly distorted by the application of different intensities in treatments of the intervention group.

Only 8 children in the OMT group and 5 children in the CCO group were in need for ventilation support. Among those 5 children in the control group occurred 1 major outlier (s. APPENDIX D). Thus, results are likely to be misleading and therefore the author refrains from further interpretation. Furthermore, the group of subjects with no need for ventilation support might represent a more valid sample (OMT: n=12, CCO: n=16) of less acute children. It may be inferred from the nearly equal outcomes that OMT does not have an impact on the recovery of children suffering from a less acute community acquired pneumonia. However, results could possibly vary with a more experienced paediatric osteopath performing OMT. A verification of these temporary results could only be provided by further research.

Very few children with a chronic heart disease (total n=6) or a chronic lung disease (total n=3) were assigned to this trial and therefore any interpretation of results is to be omitted in these two subgroups. Subjects with no additional heart disease (OMT: n=16, CCO: n=19) presented results in favour of the intervention group concerning the length of hospital stay (OMT=3.5 days, CCO=5 days) and the duration of fever (OMT=1 day, CCO=2 days) compared to that of the control group. The duration of tachypnea and time until oxygen was >90% was nearly equal comparing both groups. Still, the preliminary results of this trial showed a trend towards a positive effect of OMT on the hospital length of stay of children with acute pneumonia.

Results of the subgroup of patients with no additional chronic lung disease (OMT: n=19; CCO: n=19) showed a median of 4 days length of hospital stay in the OMT group versus a median of 5 days in the CCO group. Furthermore, the duration of fever was one day shorter in the intervention group (1 day) than in the control group (2 days), comparing the median values. While the duration of tachypnea was equal in both groups (median: 3 days), it took a day longer for children in the intervention group (median: OMT= 2 days, CCO=1 day) until they had no more

need of oxygen supply and SatO2 was >90%. No logical reason can be found why children with a longer need of oxygen supply would have a shorter length of hospital stay. Therefore, the author assumes that these results might be coincidental due to the small sample size. However, the minor trend of lower values of LOS in favour of the OMT group ask for further research.

In summary, small trends towards different directions were found in analysis of the four different subgroups. Nonetheless, most tendencies pointed towards lower values in favour of the OMT group. The group which indicates e.g. a longer hospital length of stay in the intervention group compared to that of the control group, might have occurred due to the investigator's lack of experience with osteopathy in children. Furthermore, due to the small sample sizes in these subgroups and the not normally distributed values, the power of statistical analyses of outcomes in the four groups was low and further research might lead to different results. However, no previous studies, evaluating the effect of OMT on respiratory tract infections, have ever predefined subgroups. The study on hand shows, that they might nevertheless be an interesting addition for further and more thorough research.

6.5. LIMITATIONS AND VALIDITY

The chosen study design and methodology lead to several limitations, which will be reviewed in this chapter. One limitation arose from the fact that the investigator (author) also performed the osteopathic manipulative therapy in the intervention group and was thus not blinded. Furthermore, since the researcher had a long and close relationship to Angkor Hospital for Children and its staff, it is likely that a personal desire to demonstrate a positive result, and thereby justifying this pilot trial, was present. Attempts to control bias included the standardization and outsourcing of patients' recruitment and data collection as well as the randomisation of patients' allocation via identical, sealed envelopes. Bias can still not be excluded since the personal interest of the data-collecting co-researchers is difficult to evaluate.

A weakness of this study was, that no sham group has been conducted and therefore it was impossible to evaluate the effect of the increased physical contact in the treatment group. A placebo group is therefore highly recommended for further research in this field.

As mentioned in the prior chapter, the investigator's missing experience with osteopathy in children caused further restrictions and had a possible impact on results. Attempts to control this shortcoming included a wide range of techniques to be chosen from as well as an independently adapted OMT protocol. Furthermore, some children seemed to be afraid of the foreign osteopath performing the OMT but mostly that was only at the beginning and later on the OMT seemed to be well tolerated in this acutely ill and fragile population. No child or child's caretaker complained of any side effects during the hospital stay.

A small sample size, where analyses were based on in this research, is likely to cause inaccurate results and must therefore not be disregarded. Hence, significant outcomes have to be interpreted with caution and nonsignificant trends may therefore be lacking in validity. A bigger sample size would thus serve to increase the validity of results.

The investigator would recommend to reassess the choice of the primary and secondary outcome measures for further research as well as the null hypothesis used in this present thesis. Firstly, the primary outcome measures duration of fever, duration of tachypnea and time until oxygen saturation was >90% turned out to be not stable enough to be used as a primary outcome. They might have performed more adequately as secondary outcomes or summed up as "time until clinical stability was reached". Collecting the most prominent value of the day regarding tachypnea and oxygen saturation, did not seem to be very accurate. In some cases, it was reported that a child was crying or unwell and therefore showed a certain peak value which was not necessarily representative for the day. In contrast to that, length of hospital stay as well as duration of antibiotics intake seemed to be reasonable primary outcomes and reliable tools for the recovery of pneumonia. Secondly, a single null hypothesis was constructed, which summarized all primary and secondary outcomes. Due to the large number of non-specific outcome measures, this turned out to be problematic. Although the null hypothesis can be rejected (due to one significant secondary outcome), it is still difficult to explicitly and confidentially answer the determined research question. The author would therefore recommend to modify the primary outcome measures and construct several null hypotheses to be answered independently for a more differentiated approach of the complex issue.

Although the investigator tried to be careful with the choice of the statistical tests and to be critical in their interpretation, analyses may still have caused inaccurate results because of the non-homogeneity of outcome values. Not only were the values not normally distributed, but outliers also only occurred in the control group and not in the intervention group. Non-parametric tests were therefore chosen to analyse the pre-defined subgroups, but t-tests were still conducted for analysis of numeric outcomes. This decision was based on Bortz and Döring (2010) who pointed out several Monte Carlo Studies (cf. Bonneau, 1960; Glass et al., 1972; Sawilowsky & Blair, 1992) which proved the robustness of t-tests towards non-normality. Nevertheless, the results have to be treated with caution. To minimize the impact of outliers on the result, mean and median values were calculated and analysed, and median values were given priority in case of differences between mean and median analysis of both groups.

7. CONCLUSION

The present randomized, controlled pilot study was designed to assess the effect of OMT as an adjunctive treatment to conventional clinical care only on the recovery of community-acquired pneumonia in children under the age of 5 years. Therefore, subjects were recruited at Angkor Hospital for Children, Cambodia and 41 children were randomly allocated to an OMT (n=20) and a CCO (n=21) group. All subjects received conventional clinical care for pneumonia, according to the hospital's standards and patients allocated to the OMT group received additional osteopathic manipulative treatments. Primary outcomes (hospital length of stay, duration of fever, duration of tachypnea, time until oxygen saturation was >90%) and secondary outcomes (mortality rate, frequency of nosocomial infection, duration of total-, intravenous- and oral antibiotics intake, frequency of chronic lung disease at discharge) were defined and analysed in order to help assessing the effect of OMT on the recovery of pneumonia in children. Furthermore, results of four pre-defined subgroups were analysed as part of the main study data and independently in case of differences in outcomes in these patients: radiographic pneumonia / WHO-defined clinical pneumonia only; ventilation support / no ventilation support; chronic heart disease / no chronic heart disease; and chronic lung disease (on admission) / no chronic lung disease (on admission). Chi-square tests, independent samples t-tests and Kruskal-Wallis Tests with Bonferroni's correction were conducted to determine significant differences. Mean and median values of outcome measures were calculated to compare each group and subgroup and identify trends of outcomes.

This study is the first to show that adjunctive OMT reduced the risk of nosocomial infections in children hospitalized with pneumonia. In the past, it has been hypothesized, that OMT may enhance host defences (Facto, 1947; Kimberly, 1980; Kuchera & Kuchera, 1994) and this study found some evidence to support this theory. Moreover, results indicate an effect of OMT on the recovery from childhood pneumonia, however, statistical significance could not be reached. Results from analysis of the pre-defined subgroups may specify that OMT shows the best effect on children who are severely ill.

Nevertheless, the formulated research question "DOES OMT AS AN ADJUNCTIVE TREATMENT TO CONVENTIONAL CLINICAL CARE, EFFECT RECOVERY FROM ACUTE COMMUNITY-ACQUIRED PNEUMONIA IN HOSPITALIZED CHILDREN IN CAMBODIA?" can not be answered with an explicit yes. This study provides first insights and findings into the field of osteopathy applied to children with pneumonia and may serve as a basis for further research. Trends show an impact of OMT on the recovery from childhood pneumonia and therefore open a new area of research for osteopaths. Additionally, the preliminary findings show, that OMT possibly enhances host defences to prevent nosocomial infections and could therefore present itself to be a very valuable tool, especially in intensive care units where nosocomial infections are a major problem.

If future studies focus not only on the evidence for the effectiveness of adjunctive OMT on children with pneumonia but also on the efficiency of OMT to prevent NCI, OMT may become

a common profession in hospitals. So far, only few hospitals employ osteopaths and their numbers and cases treated are not well recorded. Furthermore, this study gives osteopaths more evidence to work in the field of preventive health care. In todays time, with an aging population, preventive care is becoming increasingly more important and bears potential to save a lot of lives and costs. Preventive health care should therefore be a priority from early age on.

REFERENCES

Angkor Hospital for Children. (2016, March). Retrieved from http://angkorhospital.org

Balachandran, A., Shivbalan, S., & Thangavelu, S. (2005). Chest physiotherapy in pediatric practice. *Indian Pediatric Journal*, *42*(6), 559–68.

Beal, M. C., & Morlock, J. W. (1984). Somatic dysfunction associated with pulmonary disease. *Journal of the American Osteopathic Association*, *84*(2), 179–83.

Bonneau, C. A. (1960). The effect of violations of assumptions underlying the test. *Psychological Bulltin*, *57*, 49–64.

Bortz, J., & Döring, C. (2010). *Statistik für Human und Sozialwissenschaftler* (7th ed.). Berlin, Heidelberg: Springer-Verlag Gmbh.

Bradley, J. S., Byington, C. L., Shah, S. S., Alverson, B., Carter, E. R., Harrison, C., … Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. (2011). Executive summary: the management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clincal Infectious Diseases*, *53*(7), 617–30. http://doi.org/10.1093/cid/cir625

Bulla, A., & Hitze, K. L. (1978). Acute respiratory infections: a review. *Bulletin of the World Health Organization*, *56*(3), 481–98.

Carine, A., Mills, M., & Frymann, V. (2010). A Pediatric Perspective on Osteopathic Medicine. In C. T.P. & O. K. (Eds.), *Integrative Pediatrics* (pp. 340–363). Oxford: Oxford University Press.

Chandler, D. (2008). *A History of Cambodia* (4th ed.). Colorado, U.S.A.: Westview Press.

Cole, W. (1961). *An Introduction to Osteopathic Medicine* (2nd ed.). Kansas City, MO: Kansas City College of Osteopathy and Surgery.

Cole, W., & Pearson, W. (1949). *Outline of Osteopathic Principles* (2nd ed.). Kirksville, MO: College Press.

Connelly, L. M. (2008). Pilot Studies. *Medsurg Nursing*, *17*(6), 411–2.

Corbin, P. T. (1918). Lobar pneumonia. *Journal of Osteopathy (Kirksville)*, *25*, 141–144.

Creasy, C., Schander, A., Orlowski, A., & Hodge, L. M. (2013). Thoracic and abdominal lymphatic pump techniques inhibit the growth of S. pneumoniae bacteria in the lungs of rats. *Lymphatic Research and Biology Journal*, *11*(3), 183–6. http://doi.org/10.1089/lrb.2013.0007

Cunningham, S., Rodriguez, A., Adams, T., Boyd, K. A., Butcher, I., Enderby, B., … Lewis, S. C. (2015). Oxygen saturation targets in infants with bronchiolitis (BIDS): a double-blind, randomised, equivalence trial. *Lancet (London, England)*, *386*(9998), 1041–1048. http://doi.org/10.1016/S0140-6736(15)00163-4

Dixon, R. E. (1987). Costs of nosocomial infections and benefits of infection control programs. *Prevention and Control of Nosocomial Infections, 1st Ed. Baltimore: Williams & Wilkins*, 19–25.

Don, M. (2009, August). *Pediatric Community-Acqired Pneumonia* (Academic Dissertation). University of Tampere.

Durbin, W. J., & Stille, C. (2008). Pneumonia. *Pediatric Review Journal*, *29*(5), 147–58; quiz 159–60. http://doi.org/10.1542/pir.29-5-147

Facto, L. L. (1947). The osteopathic treatment for lobar pneumonia. *Journal of Health and Physical Education*, *18*(4), 385–92.

Fagon, J.-Y., Chastre, J., Hance, A. J., Montravers, P., Novara, A., & Gibert, C. (1993). Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. *The American Journal of Medicine*, *94*(3), 281–288.

Farha, T., & Thomson, A. H. (2005). The burden of pneumonia in children in the developed world. *Paediatric Respiratory Review*, *6*(2), 76–82. http://doi.org/10.1016/j.prrv.2005.03.001

Glass, G. V., Peckham, P. D., & Sanders, J. R. (1972). Consequences of failure to meet assumptions underlying the fixed effects analyses of variance and covariance. *Review of Educational Research*, *42*(3), 237–288.

Grebmer von, K., Headey, D., Olofinbiyi, T., Wiesmann, D., Fritschel, H., Yin, S., … Haddad, L. (2013). *Global Hunger Index. The challenge of hunger: building resilience to achieve food and nutrition security.* Bonn / Washington, DC / Dublin: International Food Policy Research

Institute; Concern Wolrdwide; Welthungerhilfe; Institute of Development Studies.

Hammer, M. C. (1947). Pneumonia: report on three cases of pneumonia treated by diet, rest, manipulation, no medication. *Osteopathic Profession*, *14*(8), 24–25,44–48.

Heiskanen-Kosma, T., Korppi, M., Jokinen, C., & Heinonen, K. (1997). Risk factors for community-acquired pneumonia in children: a population-based case-control study. *Scandinavian Journal of Infection Diseases*, *29*(3), 281–5. http://doi.org/10.3109/00365549709019043

Hertzog, M. A. (2008). Considerations in determining sample size for pilot studies. *Research in Nursing & Health*, *31*(2), 180–191.

Hodge, L. M. (2012). Osteopathic lymphatic pump techniques to enhance immunity and treat pneumonia. *Internal Journal of Osteopathic Medicine*, *15*(1), 13–21. http://doi.org/10.1016/j.ijosm.2011.11.004

Hoyt, W. J. (1947). The pneumonias: Lobar pneumonia. *Osteopathic Profession*, *14*(4), 13–18.

Hruby, R. J., & Hoffman, K. N. (2007). Avian influenza: an osteopathic component to treatment. *Osteopathic Medicine and Primary Care*, *1*, 10. http://doi.org/10.1186/1750-4732-1-10

Iregbu, K. C., & Anwaal, U. (2007). Extended spectrum Beta-Lactamase-producing Klebsiella pneumoniae septicaemia outbreak in the Neonatal Intensive Care Unit of a tertiary hospital in Nigeria. *African Journal of Medicine and Medical Sciences*, *36*(3), 225–8.

Isaac, S., & Michael, W. B. (1995). *Handbook in Research and Evaluation.* San Diego, CA: Educational and Industrial Testing Services.

Jokinen, C., Heiskanen, L., Juvonen, H., Kallinen, S., Karkola, K., Korppi, M., … Soimakallio, S. (1993). Incidence of community-acquired pneumonia in the population of four municipalities in eastern Finland. *American Journal of Epidemiology*, *137*(9), 977–88.

Julious, S. A. (2005). Sample size of 12 per group rule of thumb for a pilot study. *Pharmaceutical Statistics*, *4*(4), 287–291.

Kimberly, P. E. (1980). Formulating a prescription for osteopathic manipulative treatment. *Journal of American Osteopathic Association*, *79*(8), 506–13.

Kline, C. (1965). Osteopathic manipulative therapy, antibiotics, and supportive therapy in respiratory infections in children: comparative study. *The Journal of the American Osteopathic Association*, *65*(3), 278–278.

Kuchera, M., & Kuchera, W. (1994). Osteopathic Considerations in Systemic Dysfunction (2nd ed., pp. 33–51). Dayton, Ohio: Greyden Press, LLC.

Murphy, T. F., Henderson, F. W., Clyde, W. A., Jr., Collier, A. M., & Denny, F. W. (1981). Pneumonia: an eleven-year study in a pediatric practice. *American Journal of Epidemiology*, *113*(1), 12–21.

Noll, D. R., Degenhardt, B. F., Fossum, C., & Hensel, K. (2008). Clinical and research protocol for osteopathic manipulative treatment of elderly patients with pneumonia. *Journal of American Osteopathic Association*, *108*(9), 508–16.

Noll, D. R., Degenhardt, B. F., Morley, T. F., Blais, F. X., Hortos, K. A., Hensel, K., … Stoll, S. T. (2010). Efficacy of osteopathic manipulation as an adjunctive treatment for hospitalized patients with pneumonia: a randomized controlled trial. *Osteopathic Medicine and Primary Care*, *4*, 2. http://doi.org/10.1186/1750-4732-4-2

Noll, D. R., Johnson, J. C., Baer, R. W., & Snider, E. J. (2009). The immediate effect of individual manipulation techniques on pulmonary function measures in persons with chronic obstructive pulmonary disease. *Osteopathic Medicine of Primary Care*, *3*, 9. http://doi.org/10.1186/1750-4732-3-9

Noll, D. R., Shores, J., Bryman, P. N., & Masterson, E. V. (1999). Adjunctive osteopathic manipulative treatment in the elderly hospitalized with pneumonia: A pilot study. *The Journal of the American Osteopathic Association*, *99*(3), 143–152. http://doi.org/10.7556/jaoa.1999.99.3.143

Noll, D. R., Shores, J. H., Gamber, R. G., Herron, K. M., & Swift, J. (2000). Benefits of osteopathic manipulative treatment for hospitalized elderly patients with pneumonia. *Journal of American Osteopathic Associaton*, *100*(12), 776–82.

Paludo, C., Zhang, L., Lincho, C. S., Lemos, D. V., Real, G. G., & Bergamin, J. A. (2008). Chest physical therapy for children hospitalised with acute pneumonia: a randomised controlled trial. *Thorax*, *63*(9), 791–4. http://doi.org/10.1136/thx.2007.088195

Peck, J. F. (1948). Pneumonia: active manipulative therapy successfully used without the administation of drugs. *Osteopathic Profession*, *15*(4), 15–17,38.

Peters, D. H., Garg, A., Bloom, G., Walker, D. G., Brieger, W. R., & Hafizur Rahman, M. (2008). Poverty and Access to Health Care in Developing Countries. *Annals of the New York Academy of Sciences*, *1136*(1), 161–171. http://doi.org/10.1196/annals.1425.011

Riley, G. W. (1951). Success of osteopathy in treatment of epidemic pneumonia and influenza. *Journal of Osteopathy*, *58*(5), 14–6.

Riley, G. W. (2000). Osteopathic success in the treatment of influenza and pneumonia. 1919. *Journal of American Osteopathic Association*, *100*(5), 315–9.

Rosenthal, V. D., Bijie, H., Maki, D. G., Mehta, Y., Apisarnthanarak, A., Medeiros, E. A., … Khader, I. A. (2012). International Nosocomial Infection Control Consortium (INICC) report, data summary of 36 countries, for 2004-2009. *American Journal of Infection Control*, *40*(5), 396–407.

Rudan, I., Boschi-Pinto, C., Biloglav, Z., Mulholland, K., & Campbell, H. (2008). Epidemiology and etiology of childhood pneumonia. *Bulletin of the World Health Organization*, *86*(5), 408–16.

Sawilowsky, S. S., & Blair, R. C. (1992). A more realistic look at the robustness and Type II error properties of the t test to departures from population normality. *Psychological Bulletin*, *111*(2), 352.

Scott, J. A., Wonodi, C., Moisi, J. C., Deloria-Knoll, M., DeLuca, A. N., Karron, R. A., … Pneumonia Methods Working, G. (2012). The definition of pneumonia, the assessment of severity, and clinical standardization in the Pneumonia Etiology Research for Child Health study. *Clinical Infectious Disease Journal*, *54 Suppl 2*, S109–16. http://doi.org/10.1093/cid/cir1065

Seffinger, M. A., King, H. H., Ward, R. C., Jones, J. M., Rogers, F. J., & M, P. M. (2011). Osteopathic Philosophy. In A. G. Chila (Ed.), *Foundations of Osteopathic Medicine* (3rd ed., pp. 3–22). Philadelphia, PA: Wolters Kluwer.

Senstad, A. C., Suren, P., Brauteset, L., Eriksson, J. R., Hoiby, E. A., & Wathne, K. O. (2009). Community-acquired pneumonia (CAP) in children in Oslo, Norway. *Acta Paediatrica*, *98*(2),

332–6. http://doi.org/10.1111/j.1651-2227.2008.01088.x

Smith, R. K. (2000). One hundred thousand cases of influenza with a death rate of one-fortieth of that officially reported under conventional medical treatment. 1919. *Journal of American Osteopathic Association*, *100*(5), 320–3.

Soden, C. (1934). Treatment of pneumonia: A new analysis of the problem. *Osteopathic Profession*, *2:*, 7–9,44,46,48,50,52,54.

Still, A. T. (1910). *Osteopathy - Research and Practice*. Kirksville, MO.: Andrew Taylor Still.

Taylor JA, Beccaro M, Done S, & Winters W. (1995). EStablishing clinically relevant standards for tachypnea in febrile children younger than 2 years. *Archives of Pediatrics & Adolescent Medicine*, *149*(3), 283–287. http://doi.org/10.1001/archpedi.1995.02170150063011

Thul, P. C. (2014, September 28). Consumerism booms as Cambodia embraces once-forbidden capitalism. *Reuters*. Phnom Penh.

Torraco, R. J. (2005). Writing Integrative Literature Reviews: Guidelines and Examples. *Human Resource Development Review*, *4*(3), 356–367. http://doi.org/10.1177/1534484305278283

Transparency International. (2013). *Corruption Perceptions Index*. Retrieved from www.transparency.org

Treece, E. W., & Treece, J. W. (1982). *Elements of research in nursing* (3rd ed.). St. Lois, MO: Mosby.

Underwood, W. B. (1934). Treatment od lobar pneumonia. *Osteopathic Profession*, *1*(5), 7,25,26,28,30,32.

Vom Brocke, J., Simons, A., Niehaves, B., Riemer, K., Plattfaut, R., & Cleven, A. (2009). Reconstructing the giant: On the importance of rigour in documenting the literature search process. In *ECIS* (Vol. 9, pp. 2206–2217).

Watson, J. O., & Percival, E. N. (1939). Pneumonia research in children at Los Angeles County Osteopathic Hospital. *Journal of American Osteopathic Association*, *39*, 153–159.

Webster, J., & Watson, R. T. (2002). Analyzing the past to prepare for the future: Writing a.

MIS Quarterly, *26*(2), 13–23.

Weston, D., Klock, B., Eland, D., Harden, D., Madson, D., Gish, E., … Snide, K. (2011). Glossary of Osteopathic Terminology. *Glossary of Osteopathic Terminology*. Chevy Chase, MD: American Association of Colleges of Osteopathic Medicine.

Word Health Organization. (1995). *The management of acute respiratory infections in children* (No. 924154477 5). Geneva, Switzerland: World Health Organization.

World Health Organisation. (2015, November). Pneumonia. Retrieved from who.int

Yang, M., Yan, Y., Yin, X., Wang, B. Y., Wu, T., Liu, G. J., & Dong, B. R. (2013). Chest physiotherapy for pneumonia in adults. *Cochrane Database of Systemic Reviews*, *2*. http://doi.org/10.1002/14651858.CD006338.pub3

Yao, S., Hassani, J., Gagne, M., George, G., & Gilliar, W. (2014). Osteopathic manipulative treatment as a useful adjunctive tool for pneumonia. *Journal of Visualized Experiments*, (87). http://doi.org/10.3791/50687

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

°C degree Celsius

°F degree Fahrenheit

AFR African Region

AHC Angkor Hospital for Children

AMR American Region

CAP community-acquired pneumonia

CCO conventional care only

cf. compare

CHD chronic heart disease

CI confidence interval

CLD chronic lung disease

CP cerebral palsy

CRF case report form

CxR chest X-ray

DOF duration of fever

DOT duration of tachypnea

e.g. for example

EMR eastern Mediterranean region

EUR European Region

HIV human immunodeficiency virus

ICU intensive care unit

IRB institutional review board

ITP idiopathic thrombocytopenic purpura

ITT intention to treat

IV intravenous

LOS length of hospital stay

LT light touch

MOPSE Multicentre Osteopathic Pneumonia Study in Elderly

n number

NCI nosocomial infection

OMM Osteopathic Manipulative Medicine

OMT Osteopathic Manipulative Treatment

PO oral

PP per-protocol

RRI recurrent respiratory infection

RSV respiratory syncytial virus

s. see

SatO2 oxygen saturation

SD standard deviation

SDF somatic dysfunction

SEAR South-East Asia Region

SPSS statistic package of the social science

URTI upper respiratory tract infection

VS ventilation support

vs. versus

WHO The World Health Organization

WPR Western Pacific Region

APPENDICES

APPENDIX A: INTERNATIONAL REVIEW BOARD (IRB) - ETHIC APPROVAL

ANGKOR HOSPITAL FOR CHILDREN

មន្ទីរពេទ្យកុមារអង្គរ

Preah Sangkeach Tep Vong Road & Umchhay Street, Mondul 1, Sangkat Svay Dangkum P.O. Box 50, Siem Reap, Kingdom of Cambodia
Tel: (855) 63 963 409 Fax: (855) 63 760 452 Email: admin@angkorhospital.org http://www.angkorhospital.org

Ref No. 0033/16 AHC

January 08th, 2016

Ms. Theresia Orsini-Rosenberg
Osteopath, Dipl. PT
Grindelberg 81, 20144 Hamburg, Germany
AHC, PO Box 50, Siem Reap, Cambodia
Email: t.orsinirosenberg@gmail.com

Re: **"The Effectiveness of Osteopathic Manipulation (OMT) as Adjunctive Treatment on hospitalized Children with Acute Pneumonia. – A Randomized Controlled Trial"**

Dear Ms. Theresia,

Institutional Review Board of Angkor Hospital for Children (AHC IRB), has considered and approved your protocol entitled "**The Effectiveness of Osteopathic Manipulation (OMT) as Adjunctive Treatment on hospitalized Children with Acute Pneumonia. – A Randomized Controlled Trial"** through the expedited review on December 22, 2015 and additional clarification with principal investigator.

This approval is valid for a period of twelve months after the approval date and you need to resubmit the proposal and brief progress report two weeks before expiry date for renewal.

AHC IRB requires that your team report any serious adverse events (SAE) to our IRB within 1 week of discovery. SAE are any unexpected events that:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity

If you have any questions concerning this information, please contact Human Protections Administrator via the email: purchaser2@angkorhospital.org

Sincerely yours,

Duong Vibol
Chairperson
Institutional Review Board
Angkor Hospital for Children

Dr. Ngoun Chanpheaktra
Hospital Director
Angkor Hospital for Children

APPENDIX B: HAND-OUTS FOR PATIENTS AND STAFF

INFORMATION SHEET (ENGLISH) FOR PATIENTS' CARETAKERS

STUDY TITEL: **The Effectiveness of Osteopathic Manipulation (OMT) as Adjunctive Treatment on hospitalized Children with Acute Pneumonia. – A Randomized Controlled Trial.**

Your child is being asked to join a research study of patients being presented to the Angkor Hospital for Children, suffering from acute Pneumonia. This sheet tells you about the study and the disease. You can ask the interviewer any questions you might have at any time.

WHAT IS THE PURPOSE OF THE STUDY?

Pneumonia is a form of acute respiratory infection that affects the lungs. When an individual has pneumonia, the small sacs in the lung – called alveoli – are filled with pus and fluid, which makes breathing painful and limits oxygen intake. It affects children and families worldwide and is therefore an important disease to study in order to improve therapy.

Pneumonia should be treated with antibiotics, which the doctor should already have prescribed to your child. Furthermore, oxygen supply might be needed and good nutrition and positioning your child is important. Studies on adults in the USA have shown, that a therapy called "Osteopathic Manipulative Treatment" also improves the health of a person suffering from pneumonia by reducing the length of hospital stay (LOS). Since there is a higher risk of germ infection while staying in a hospital, rather than being at home, reducing the LOS might be a useful additional treatment strategy.

The purpose of this study is to find out if regular Osteopathic Manipulative Treatments as additional therapy can have a positive effect on your child's health. This is important to know in order to improve the standard therapy for children suffering from acute pneumonia in the future.

DOES YOUR CHILD HAVE TO TAKE PART?

It is entirely up to you and your child to decide whether or not to take part. If you decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you do not want to take part, your child will still receive appropriate medical care from AHC.

WHAT ARE WE ASKING YOU AND YOUR CHILD TO DO?

You will be asked some questions and will be asked to give consent for our staff to collect data from your child's medical records that relates to this study. We would like to know some general information about your child like age, sex, birth weight, nutrition status and maternal smoking and/or any history of tuberculosis in the family. You or your child can choose not to answer any of these questions for any reason; just say so and we will move on to the next question.

Your child will then be randomly allocated to the intervention or control group.

WHAT IS THE DIFFERENCE BETWEEN THE INTERVENTION AND THE CONTROL GROUP?

As the purpose of the study is to find out which treatment is the best, there is no better or worse group to be in.

The intervention group will receive OMT once a day, 5 days per week plus standard treatment for pneumonia until discharge. The control group will receive standard treatment for pneumonia alone. Ms. Theresia, a certified and experienced osteopath will administer OMT to all patients of the intervention group.

The patients, regardless of trial group, will all receive standard AHC clinical care.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF TAKING PART?

We hope that the information gained from this study will help us to care for patients more effectively in the future. Any further diseases or problems that are discovered by this study will also be treated according to standard care.

Some techniques of OMT might tickle or hurt a little bit, like you can sometimes feel during a light massage and/or might increase secretion. This is a good sign, because the lung clears up faster, but it might lead to suction or increased coughing. Suction is part of your child's standard care.

WHAT IF YOU CHANGE YOUR MIND?

You have the right to ask questions at any time. If you agree to participate in the study, you can change your mind and withdraw at any time and for any reason. You do not have to tell us the reason and the care your child receives will not be affected by this decision.

WHAT IF SOMETHING GOES WRONG?

As OMT is a non-invasive therapy and mainly aims to support the immune system of you child, it is very unlikely that problems may occur. However, if any problems do arise, the study team will take care of any problems and will be responsible for any costs for further treatment.

CONFIDENTIALITY

All information will be kept confidential by the study team. No identifying patient information like your child's name will be shared with other people. Only the investigators and research nurses directly responsible for this project can access your child's information.

WHO HAS REVIEWED THE STUDY?

This study has been reviewed and approved by the Research Approval Committee and the Ethics Committee (IRB) of Angkor Hospital for Children.

You or your child can contact the following people at any time if your child develops problems or you have questions relating to the study:

Mr. Tan Sethy (Tel: 063 963 409 / Mobile: 089 642 183)

Mr. Chea Sothorn (Mobil: 017 710 110)

Ms. Theresia Orsini-Rosenberg (Mobile: 096 312 71 81)

CONSENT FORM (ENGLISH) FOR PATIENTS' CARETAKERS

STUDY TITEL: The Effectiveness of Osteopathic Manipulation (OMT) as Adjunctive Treatment on hospitalized Children with Acute Pneumonia. – A Randomized Controlled Trial.

PATIENT LABEL	Date of Enrolment I___I___I – I___I___I – 20 I___I___I

I understand and have been given an information sheet on this research study and have discussed the study with

_____
(name of research worker)

☐ I understand the purpose of the study and why my child has been chosen.

☐ I understand that my child does not have to take part in the study.

☐ I understand the procedures and treatments involved in this study, including the intervention and control groups.

☐ I understand the possible risks, any discomfort involved, and anticipated length of time and the frequency with which the procedures will be performed.

☐ I understand that even if I agree now, I can still withdraw my child from the study at any time for any reason; and that my child will still receive proper care in this hospital if I withdraw.

☐ I understand that the researchers will take responsibility for any harm or complications that may arise as a result of study procedures without any cost to me.

☐ I understand that my child's information will be kept confidential and my child's personal information will not be shared with outside people.

☐ I understand that my child's involvement in this research project may not be of any direct benefit to my child.

☐ I have been given names and telephone numbers of researchers I can contact in case of any questions or problems.

☐ I understand the information given to me and hereby agree my child to participate in this research study.

.....Parent/Caretaker Date: ……./……/……

.....Researcher Date: ……./……/……

.....Witness Date: ……./……/……

INFORMATION SHEET AND CONSENT FORM (KHMER) FOR PATIENTS' CARETAKERS

ព្រឹត្តិបត្រព័ត៌មាន

ការវាយតម្លៃអំពីប្រសិទ្ធភាពនៃការព្យាបាលដោយ Osteopathic Manipulative Treatment ទៅលើកុមារដែលមានជំងឺសួតស្រួចស្រាវ

កូនរបស់លោកអ្នកត្រូវបានស្នើសុំឲ្យចូលរួមការសិក្សាស្រាវជ្រាវមួយ ដែលកំឡុងពេលដែលពួកគេ
កំពុងសំរាកព្យាបាលជំងឺនៅក្នុងមន្ទីរពេទ្យកុមារអង្គរដែលមានបញ្ហាពីការរលាកសួតស្រួចស្រាវ។
ព្រឹត្តិបត្រព័ត៌មាននេះប្រាប់លោកអ្នកអំពីការសិក្សានិងជំងឺ។ លោកអ្នកអាចសួរសំណួរទៅកាន់
អ្នកសម្ភាសន៍សបានគ្រប់ពេលវេលាប្រសិនបើមាន:

១. តើអ្វីទៅគឺជាគោលបំណងនៃការសិក្សាស្រាវជ្រាវ?

ជំងឺរលាកសួត គឺ ជាប្រភេទជំងឺមួយដែលមានការបង្កហេតស្រួចស្រាវទៅលើផ្លូវដង្ហើមដែលបង្កឲ្យមានផលប៉ះពាល់ដល់សួត។ នៅពេលដែលមនុស្សម្នាក់ឮមានជំងឺរលាកសួត កូនចង្កឹះដែលនៅស្ថិតក្នុងសួតដែលគេឲ្យឈ្មោះថា**alveoli**គឺពោពេញទៅដោយខ្លួននិងវត្តមាន(ទឹក)ដែលជាមូលហេតុមួយធ្វើឲ្យការដកដង្ហើមមានការឈឺចាប់និងកម្រិតការស្រូបចូលអុកស៊ីសែនទៅក្នុងសួត។ វាធ្វើឲ្យមានផលប៉ះពាល់ដល់ក្រុមគ្រួសារនិងកុមារទូទាំងពិភពលោកយើងនេះ។ដូចនេះហើយបានជាការសិក្សាស្រាវជ្រាវអំពីជំងឺនេះគឺមានសារៈសំខាន់ណាស់ដើម្បីរៀបចំធ្វើឲ្យមានការព្យាបាលមួយឲ្យកាន់តែមានប្រសិទ្ធភាព។

ជំងឺរលាកសួតត្រូវបានព្យាបាលដោយថ្នាំផ្សះទៅតាមកូនរបស់លោកអ្នកដែលត្រូវធ្វើឡើងតាមវេជ្ជបញ្ជារបស់ត្រូពេទ្យ។ បន្ថែមពីលើនេះទៀត កូនរបស់លោកអ្នកប្រហែលជាត្រូវការផ្តល់អុកស៊ីសែនជំនួយ អាហារូបត្ថម្ភនិង ការរៀបចំស្ថានភាពគឺជាការចាំបាច់។ ការសិក្សាស្រាវជ្រាវមួយទៅលើមនុស្សពេញវ័យ
នៅក្នុងប្រទេសអាមេរិច ដែលគេឲ្យឈ្មោះថា "Osteopathic Manipulative Treatment"
បានបង្ហាញឲ្យឃើញថាមានភាពប្រសើរចំពោះអ្នកជំងឺរលាកសួតដូចជាការកាត់បន្ថយរយៈពេលនៃការស្នាក់នៅក្នុងមន្ទីរពេទ្យកំឡុងពេលដែលសំរាកព្យាលក្នុងមន្ទីរពេទ្យថាប់តាំងពីមានការបង្អកដង្ហើមកម្រិតធ្ងន់ធ្ងរមកជាជាងការស្នាក់នៅក្នុងមន្ទីរពេទ្យដូចជាការនៅផ្ទះ។ការកាត់បន្ថយរយៈពេលនៃការស្នាក់នៅក្នុងមន្ទីរពេទ្យគឺជាវិធីសាស្ត្រនៃការព្យាបាលដ៏ប្រសើរបន្ថែមទៀត។
ដូច្នេះគោលបំណងនៃការសិក្សានេះគឺដើម្បីស្វែងរកឲ្យឃើញថាការព្យាបាលបន្ថែមដោយទៀងទាត់ជាមួយ OsteopathicManipulative Treatments ពិតជាអាចមានប្រសិទ្ធភាពលើសុខភាពរបស់កុមារ។
ហេតុដូចនេះហើយវាមានសារៈសំខាន់ណាស់ដើម្បីនឹងក្នុងការធ្វើឲ្យកាន់តែប្រសើរលើគុណភាពនៃការព្យាបាលជាសូដាមួយសំរាប់កុមារដែលមានជំងឺរលាកសួតស្រួចស្រាវទៅថ្ងៃអនាគត។

២. តើកូនៗរបស់លោកអ្នកត្រូវតែចូលរួមឬទេ?

វាគឺអាស្រ័យទៅលើលោកអ្នកនិងកូនរបស់លោកអ្នកថាតើត្រូវតែចូលរួមឬមិនចង់ចូលរួម។

- ប្រសិនបើលោកអ្នកសំរេចចិត្តថាចូលរួមក្នុងការសិក្សាស្រាវជ្រាវនេះ។លោកអ្នកនឹងត្រូវបានផ្តល់ឲ្យនូវព្រឹត្តិបត្រព័ត៌មានដើម្បីរក្សាទុកនិងស្នើសុំអនុញ្ញាតឲ្យចុះហត្ថលេខាយល់ព្រមនៅលើកិច្ចសន្យានេះ។
- ប្រសិនបើលោកអ្នកមិនចង់ចូលរួមក្នុងការសិក្សាស្រាវជ្រាវនេះទេ កូនរបស់លោកអ្នកនៅតែអាចទទួលបាននូវការព្យាបាលនិងថែទាំដ៏សមស្របពីមន្ទីរពេទ្យកុមារអង្គរតដែល។

៣. តើអ្វីខ្លះដែលយើងនឹងសួរទៅអ្នកនិងស្នើសុំឲ្យកូនរបស់លោកអ្នកធ្វើ?

លោកអ្នកនិងត្រូវបានសួរនូវសំណួរខ្លះៗ និងស្នើសុំការអនុញ្ញាតឲ្យបុគ្គលិករបស់យើងខ្ញុំ

បានប្រមូលព័ត៌មានពីកំណត់ត្រាឯកសាររបស់កូនលោកអ្នកដែលទាក់ទងនឹងការសិក្សាស្រាវជ្រាវនេះ។ ពួកយើងត្រូវការនឹងនូវព័ត៌មានទូទៅមួយចំនួនពីកូនរបស់លោកអ្នកដូចជា: អាយុ ភេទ ទម្ងន់កើត ស្ថានភាពអាហារូបត្ថម្ភ ប្រវត្តិនៃការឆក់ជាវីឬក៍ក្រុមត្រួសារមានកើតជំងឺរបេង។
លោកអ្នកអាចជ្រើសរើសឆ្លើយឬមិនឆ្លើយនិងសំណួរណាមួយដោយមានហេតុផលបានគ្រាន់តែនិយាយថាទេ នោះយើងនិងរំលងទៅសំនួរបន្ទាប់ទៀត។ ជាបន្ទាប់ទៀតកូនរបស់លោកអ្នកនឹងត់រូវឲ្យចាប់ផ្តោតថាតើស្ថិតនៅក្នុងក្រុមអន្តរាគមន៍(ព្យាបាល) ឬក៍ត្រួតពិនិត្យ។

៤. តើអ្វីទៅជាភាពខុសគ្នារវាងក្រុមអន្តរាគមន៍ និង ត្រួតពិនិត្យ?

គោលបំណងនៃការសិក្សាគឺដើម្បីស្វែងរកឲ្យឃើញថាការព្យាបាលមួយណាដែលល្អជាងគេ។ ទាំងអស់នេះពុំមានន័យថាល្អ ឬអាក្រក់ក្នុងក្រុមនីមួយៗឡើយ។ ក្រុមអន្តរាគមន៍និងទទួលបានការធ្វើដោ OMTក្នុងមួយថ្ងៃម្តងមានប្រាំថ្ងៃក្នុងមួយសប្តាហ៍រួមបញ្ចូលសុង់ដាព្យាបាលសំរាប់ការលាកសួតរហូតទាល់តែអ្នកជំងឺចេញពីមន្ទីរពេទ្យ។ក្រុមត្រួតពិនិត្រនិងទទួលបានសុង់ដាព្យាបាលសំរាប់ការលាកសួតតែឯង(ធម្មតា)។ **អ្នកនាង គេមសៀរ** ដែលមានសញ្ញាបត្រនិងបទពិសោធន៍ osteopathy និងធ្វើការព្យាបាលដោយប្រើ OMTទៅដល់គ្រប់អ្នកជំងឺទាំងអស់ដែលស្ថិតក្នុងក្រុមអន្តរាគមន៍(ព្យាបាល)។ គ្រប់អ្នកជំងឺទាំងអស់ថ្វីបើមិនបានធ្វើនៅក្នុងក្រុមសាកល្បង តែនឹងទទួលបានការព្យាបាលថែទាំទៅតាមសុង់ដារបស់មន្ទីរពេទ្យកុមារអង្គរ។

៥. តើអ្វីទៅគឺជាផលប្រយោជន៍វិជ្ជមាននិងផលប្រយោជន៍អវិជ្ជមាននៃការចូលរួមធ្វើការសិក្សា?

យើងសង្ឃឹមថាព័ត៌មានដែលបានមកពីការសិក្សានេះនិងជួយឲ្យយើងធ្វើការថែទាំអ្នកជំងឺកាន់តែមានប្រសិទ្ធភាពទៅថ្ងៃអនាគត។ ជំងឺផ្សេងៗឬក៍បញ្ហាដែលបានរកឃើញតាមរយៈការសិក្សាស្រាវជ្រាវនេះនិងត្រូវបានព្យាបាលទៅតាមសុង់ដានៃការថែទាំ។ ពេលខ្លះនៃបច្ចេកទេសរបស់ OMT ប្រហែលជាធ្វើឲ្យរលើបឬមានការឈឺចាប់តិចតួចដូចជាមានអារម្មណ៍ថាការរិតច្រេចាច់សើរៗឬប្រហែលជាមានការកើនឡើងស្លេសនេះគឺជាសញ្ញាល្អមួយពីព្រោះសួតសម្អាតបានរហ័សប៉ុន្តែវាអាចធ្វើឲ្យក្អកកើនឡើងឬត្រូវការបូមស្លេស។ ការបូមស្លេសគឺជាផ្នែកមួយនៃសុង់ដាថែទាំដែរ។

៦. ប្រសិនបើលោកអ្នកប្តូរចិត្តរបស់លោកអ្នកពីការសិក្សានេះតើមានរឿងអ្វីទេ?

លោកអ្នកមានសិទ្ធគ្រប់គ្រាន់ដើម្បីយល់ព្រមចូលរួមក្នុងការសិក្សា ឬ លោកអ្នកអាចផ្លាស់ប្តូរចិត្តបញ្ឈប់ការចូលរួមការសិក្សានេះដោយមានហេតុផលណាមួយដោយពុំចាំបាច់ប្រាប់យើងពីហេតុផលនោះទេហើយការការថែទាំដែលកូនរបស់លោកអ្នកបានទទួលនឹងមិនប៉ះពាល់ដល់ការសម្រេចចិត្តឈប់របស់លោកអ្នកទេ។

៧. ប្រសិនបើមានអ្វីមួយធ្វើខុសតើមានរឿងអ្វីទេ?

OMTគឺមិនមែនជាការព្យាបាលមួយដែលធ្វើឲ្យមានការរាគក្អាកទេ។ គោលបំណងសំខាន់នៃការព្យាបាលគឺដើម្បីជួយទ្រទ្រង់ដល់ប្រព័ន្ធភាពស៊ាំនិងភេតរបស់កូនលោកអ្នក។ វាមិនទំនងនឹងធ្វើឲ្យមានបញ្ហាកើតឡើងទេ។ ទោះបីជាយ៉ាងណាក៍ដោយប្រសិនបើមានបញ្ហាកើតឡើងក្រុមសិក្សាស្រាវជ្រាវនិងមើលថែរាល់បញ្ហាដែលមាននិងទទួលខុសត្រូវរាល់តម្លៃសំរាប់ការព្យាបាលខាងមុខ។

៨. ភាពជាសម្ងាត់

គ្រប់ព័ត៌មានទាំងអស់និងត្រូវបានរក្សាទុកជាការសម្ងាត់ដោយក្រុមសិក្សាស្រាវជ្រាវ។ មិនមានការសំគាល់ពីព័ត៌មានជំងឺដូចជាឈ្មោះរបស់កូនលោកអ្នកត្រូវបានចែកចាយទៅដល់អ្នកដទៃបានឡើងទៀតទេ។ព័ត៌មានពីកូនរបស់លោកអ្នកត្រូវបានដឹងដោយអ្នកអង្កេតពិនិត្យនិងតំលានុបដ្ឋាយិការដែលទទួលខុសត្រូវដោយផ្ទាល់ចំពោះគម្រោងនេះតែប៉ុណ្ណោះ។

៩. នរណាខ្លះដែលត្រួតពិនិត្យមើលលើការសិក្សា?

ការសិក្សានេះត្រូវបានត្រួតពិនិត្យមើលឡើងវិញនិងយល់ព្រមដោយគណ:កម្មការផ្នែកស្រាវជ្រាវនិងគណ:កម្មការត្រួតពិនិត្យក្រមសីលធំម៌ការសិក្សាស្រាវជ្រាវរបស់ស្ថាប័នមន្ទីរពេទ្យកុមារអង្គរ ។លោកអ្នកឬកូនរបស់លោកអ្នកអាចធ្វើការទាក់ទងគ្រប់ពេលវេលាអំពីការវិវត្តន៍នៃបញ្ហាកូនរបស់លោកអ្នកឬក៍មានសំណួរដែលមានការទាក់ទងនឹងការសិក្សានេះ។

១. គេមសៀរ អរសិនន៏ រ្សសិនបឹក

២. គាន់ សេន្ធី ០៨៩ ៦៥២ ១៨៣

៣. ជា សុផន ០៧៧ ៧០៦ ៦០៧

កិច្ចសន្យាចូលរួមក្នុងការសិក្សាស្រាវជ្រាវ

ការវាយតម្លៃពីប្រសិទ្ធភាពនៃការព្យាបាលដោយ OSTEOPATHIC MANIPULATIVE TREATMENT

(OMT) ទៅលើកុមារដែលមានជំងឺរលាកសួតស្រួចស្រាវ

លេខសម្គាល់ការសិក្សា..... ថ្ងៃ ...../ខែ...../ឆ្នាំ.....

ខ្ញុំបានយល់ដឹងនិងទទួលនូវព្រឹត្តិបត្រព័ត៌មានព្រមទាំងបានធ្វើការពិភាក្សាស្តីពីការសិក្សាស្រាវជ្រាវនេះជាមួយ

_____

(ឈ្មោះរបស់អ្នកស្រាវជ្រាវ)

☐ ខ្ញុំបានដឹងពីគោលបំណងនិងហេតុផ្នែបានជាកូនរបស់ខ្ញុំត្រូវបានជ្រើសរើសក្នុងការសិក្សា

☐ ខ្ញុំបានដឹងដែលថាកូនរបស់ខ្ញុំមិនត្រូវដាច់ខាតឲ្យចូលរួមក្នុងផ្នែកសិក្សា

☐ ខ្ញុំបានដឹងពីទម្រង់ការនិងការព្យាបាលដែលទាក់ទងនិងការសិក្សានេះដោយរាប់បញ្ចូលក្រុមអន្តរាគមន៍(ព្យាបាល) និង ក្រុមត្រួតពិនិត្យ។

☐ ខ្ញុំបានដឹងពីហានិយភ័យដែលទាក់ទងភាពមិនស្រួលណាមួយនិងប្រមើលពីរយៈពេលដ៏វែងហើយនិងភាពញឹកញាប់ដែលនឹងត្រូវបានធ្វើជាមួយនិងទម្រង់ការ ។

☐ ខ្ញុំបានដឹងដែរថាប្រសិនបើខ្ញុំយល់ព្រមឥឡូវនេះ ហើយខ្ញុំក៏នៅតែអាចសុំឲ្យកូនរបស់ខ្ញុំបញ្ឈប់ការសិក្សាសម្រាប់ហេតុផលមួយ។ កូនរបស់ខ្ញុំក៏នៅតែទទួលបានការព្យាបាលដ៏សមរម្យនៅក្នុងមន្ទីរពេទ្យដដែល។

☐ខ្ញុំបានដឹងដែរថាអ្នកស្រាវជ្រាវនឹងមានការទទួលខុសត្រូវចំពោះតម្លៃនៃការព្យាបាលបន្ទុក បន្ទាប់ពីមានគ្រោះថ្នាក់ឬផលលំបាកដែលអាចកើតមានឡើងតាមរយៈការសិក្សា

☐ខ្ញុំបានដឹងថារាល់ព័ត៌មានដែលជាប់ទាក់ទងនឹងកូនរបស់ខ្ញុំវានិងត្រូវរក្សាទុកជាសម្ងាត់ដោយមិនត្រូវបានអនុញ្ញាតិឲ្យបុគ្គលដ៏ទៃទៀតបានដឹងឡើយ។

☐ខ្ញុំបានដឹងថាការជាប់ទាក់ទងនិងគម្រោងសិក្សានេះប្រហែលជាមិនអាចបានផលប្រយោជន៍ដោយផ្ទាល់ដល់កូនរបស់ខ្ញុំទេ។

☐ខ្ញុំត្រូវបានឲ្យស្គាល់នូវឈ្មោះនិងលេខទូរសព្ទ័របស់អ្នកសិក្សាស្រាវជ្រាវដើម្បីងាយស្រួលធ្វើការទាក់ទងប្រសិនបើមានសំនួរឬមានបញ្ហា។.

☐ខ្ញុំបានដឹងពីព័ត៌មានដែលបានផ្តល់ទៅខ្ញុំនិងបានយល់ព្រមឲកូនរបស់ខ្ញុំចូលរួមការសិក្សាស្រាវជ្រាវនេះ។

.....អ្នកជំងឺ/អ្នកថែទាំ ថ្ងៃ ...../ខែ...../ឆ្នាំ.....

.....អ្នកស្រាវជ្រាវ ថ្ងៃ ...../ខែ...../ឆ្នាំ.....

.....សាក្សី ថ្ងៃ ...../ខែ...../ឆ្នាំ.....

AHC STAFF INFORMATION SHEET

Dear AHC staff,

may I inform you about the new research, starting on Monday, January 11th, on **patients between 0-5**, admitted to IPD, ICU, LAU and SU **diagnosed with pneumonia** (X-ray findings and/or WHO definition):

WHAT IS OSTEOPATHY / OSTEOPATHIC MANIPULATIVE TREATMENT?

Osteopathic Manipulative Treatment (OMT) is a non-pharmacologic manual therapy which was developed in the late 19th century before the use of antibiotics. The intention was to treat infections (like pneumonia) by improving host defences. Although this is the past, repeated observations show correlated visceral diseases with abnormal structural findings like positional asymmetry of bony landmarks, restricted joint motion, tissue congestion, muscle tightness and palpatory tenderness. It is hypothesised that these abnormal structural findings of the musculoskeletal system may influence the body's ability to recover. The Osteopath manually treats these abnormal structural findings in order to support the patient's recovery.

WHO SHOULD BE IN THIS STUDY?

Patients

- from **0-5 years**
- **diagnosed with Pneumonia** (WHO definition and/or x-ray findings)
- **admitted to IPD, ICU, LAU or SU** for 12 hours.

WHAT WILL BE DONE?

If a patient fulfils the criteria mentioned above, the patient should be referred to Physiotherapy. Mr Tan Sethy or Mr. Chea Sothorn will then inform the caretaker about the study. If the caretaker gives consent, the patient will be enrolled.

The study includes one intervention and one control group. The **intervention group** receives OMT five times per week plus standard clinical care (including but not limited to: medication, cultures, ventilation, positioning, suction, etc.), **excluding chest-physiotherapy**. OMT will only be performed by Theresia, the research and Osteopath volunteer at AHC.

The **control group** will receive standard clinical care alone (including but not limited to: medication, ventilation, positioning, suction, etc.) without any manual therapy such as OMT and/or CPT.

WHAT ARE THE ENDPOINTS OF THE STUDY?

Among other aspects we will assess all causes of mortality attributed mainly to respiratory failure, the length of hospital stay, the duration of fever and the time until oxygen is >92.

RISKS OR DISCOMFORT FOR THE PATIENT:

OMT may increase the expulsion of secretions, which may lead to temporary discomfort of the patient, and possibly increased suctioning of the airways. Suction (if needed) can lead to a vagal response. However, this is also part of the routine care.

WHAT WILL AHC STAFF HAVE TO DO?

Please refer patients (age 0-5) diagnosed with pneumonia to Physiotherapy and/or so that we don't miss enrolling someone.

Mr. Tan Sethy, Mr. Chea Sothorn and I will be around on the different wards as much as possible. **FOR FURTHER QUESTIONS, PLEASE ASK ANY OF US AT ANY TIME.**

Thank you!! Theresia (mobile: 096 312 7181)

APPENDIX C: DOCUMENTATION FORMS

CASE REPORT FORM (CRF) OF THE OMT-STUDY

Study Title: **The Effectiveness of Osteopathic Manipulation (OMT) as Adjunctive Treatment on hospitalized Children with Acute Pneumonia. – A Randomized Controlled Trial.**

Patient details

AHC ID I___I___I___I___I – I___I___I___I___I___I___I___I___I

Date of Enrolment I___I___I – I___I___I – 20 I___I___I

DOB I___I___I – I___I___I – 20 I___I___I

Gender ☐ Male ☐ Female ☐ Unknown

Ward ☐ IPD ☐ ICU ☐ LAU ☐ SU

1. Inclusion Criteria (tick closes boxes in appropriate column)	NO	YES
. Age 0-5 years	☐	☐
. Admitted to AHC for more than 12h	☐	☐
. Diagnosed with Pneumonia (WHO)	☐	☐
. Informed consent was signed	☐	☐
If any of the above are answered NO, the child CAN NOT enter the study.		

2. Eligibility Summary	NO	YES
. Is participant eligible for the study?	☐	☐
. Was informed consent given to participant?	☐	☐
If NO, specify reason: _____		
Date, study informed consent was signed I___I___I – I___I___I – 20 I___I___I		

3. Enrolment Summary	NO	YES
. Is participant being enrolled?	☐	☐
If NO, Reason for NOT enrolled:		
. ☐ Did not meet eligibility criteria		
. ☐ Met eligibility criteria but refused to participate		

- ☐ Met eligibility criteria, gave consent, but refused for other reasons
- ☐ Missed by admitting team and investigators

4. Was the patient already subjected to standard pneumonia treatment?	NO	YES
	☐	☐

5. General Information

Low birth weight (<2000g)	NO ☐ YES ☐	If YES, how much? _____
Prematurity	NO ☐ YES ☐	
Maternal smoking	NO ☐ YES ☐	
History of TB in the family	NO ☐ YES ☐	If YES, who? _____
Admitted to ICU	NO ☐ YES ☐	
Malnutrition	NO ☐ YES ☐	If YES, what stage?_____
Chronic illness (incl. But not limited to HIV, chronic lung disease, etc.)	NO ☐ YES ☐	If, YES, what? _____

6. Chest radiographic findings NO ☐ YES ☐

Consolidation	NO ☐ YES ☐	If YES, where?_____
Atelectasis	NO ☐ YES ☐	If Yes, Grade? _____
Hyperinflation	NO ☐ YES ☐	If YES, where? _____
Pleural Effusion	NO ☐ YES ☐	If YES, where? _____
Tuberculosis	NO ☐ YES ☐	
Cardiac failure	NO ☐ YES ☐	If YES, what?_____

OUTCOME SUMMARY

OUTCOMES SUMMARY:	**PATIENT HOSPITAL REGISTRATION NO:** ___ ___ ___ ___ - ___ ___ ___ ___ ___ ___ ___

Date of discharge: (dd/mm/yy) ___ ___/___ ___/___ ___

a. Did Participant survive? NO ☐ YES ☐

- If NO, date of DEATH (dd/mm/yy) __ __/__ __/__ __
- If NO, cause of death, if known: _____

b. Length of total admission _____ days

c. Total duration of fever _____ days

d. Duration of tachypnea _____ days

e. Time until O2-Sat > 92% w/o oxygen supply _____ days

f. Need for ventilation support or continuous positive airway pressure? NO ☐ YES ☐
If YES, days: _____

g. Did Patient have / develop a nosocomial infection during hospital stay? NO ☐ YES ☐

h. Was the patient diagnosed with chronic lung disease on discharge? NO ☐ YES ☐

CLINICAL INVESTIGATOR'S STATEMENT (TOR, TS, YK)
I have reviewed all data contained on the case report forms for this patient and have verified that the patient got the appropriate treatment according to his group. The report forms truly reflect the Patient's condition before, during and at the completion of the study. _____ _____ ___ ___ / ___ ___ / ___ ___ ___ ___ **Investigator Initials** **Investigator Signature**

DAILY ASSESSMENT FORM

AHC - OMT STUDY – DAILY ASSESSMENT FORM

PATIENT'S HOSPITAL REGISTRATION NUMBER: _ _ _ _ _ - _ _ _ _ _ _ _ _

- Please check respiratory symptoms and signs 1x/day before therapy and **mark Y = YES or N = NO with √**
- Please check auscultation sounds 1x/day before therapy and **mark the appropriate sign with √**
- Please mark type of ventilation 1x/day before therapy as followed with √:

Mech. Vent = mechanical ventilation support, CPAP = Continuous positive airway pressure, O2 = Oxygen supply only, Non = no support

- Please **mark *NC Inf.* with √** if Pt has or develops a ***nosocomial infection*** during his hospital stay.

No	Date	RESPIRATORY SYMPTOMES AND SIGNS										AUSCULTATION					VENTILATION				
DAY		Coughing		Fever		Resp. Rate normal for age		O2-Sat > 92		Chest in drawings		Fine crackle	Coarse crackle	Rhonchi	Wheezes	Non	M. Vent	C-PAP	O2	Non	NC. Inf.
		Y	N	Y	N	Y	N	Y	N	Y	N										
1																					
2																					
3																					
4																					
5																					
6																					
7																					
8																					
9																					
10																					
11																					
12																					
13																					
14																					
15																					

THERAPY DOCUMENTATION FORM

AHC – OMT STUDY - THERAPY FORM

Patient is part of

☐ **the INTERVENTION GROUP**

- Please mark D. Ass with √ for finishing the daily assessment.
- Please mark OMT with √ for finishing therapy.

Day	Date	D. Ass	OMT	Notes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				

PT'S HOSPITAL REGISTRATION NO: _ _ _ _ - _ _ _ _ _ _ _

☐ **the CONTROL GROUP**

- Please note D. Ass with √ for finishing the daily assessment.

Day	Date	D.Ass.	Notes
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			

APPENDIX D: STATISTICS

NORMAL DISTRIBUTION TEST (SHAPIRO-WILK-TEST) for values of LOF, DOF, DOT, SatO2, total antibiotic intake, IV antibiotic intake and PO antibiotic intake

Tests auf Normalverteilung

		Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Group	Statistik	df	Signifikanz	Statistik	df	Signifikanz
LOSd	CCO	,288	21	,000	,523	21	,000
	OMT	,229	20	,007	,873	20	,013
DOFd	CCO	,273	21	,000	,844	21	,003
	OMT	,207	20	,024	,899	20	,039
DOTd	CCO	,309	21	,000	,492	21	,000
	OMT	,221	20	,012	,807	20	,001
SatO2d	CCO	,324	21	,000	,478	21	,000
	OMT	,216	20	,016	,847	20	,005
ABTotald	CCO	,230	21	,005	,834	21	,002
	OMT	,296	20	,000	,778	20	,000
ABIVd	CCO	,206	21	,021	,851	21	,004
	OMT	,265	20	,001	,840	20	,004
ABPOd	CCO	,404	21	,000	,682	21	,000
	OMT	,280	20	,000	,812	20	,001

a. Signifikanzkorrektur nach Lilliefors

BOXPLOT OF OUTLIERS IN THE SUBGROUP: VS AND NO VS