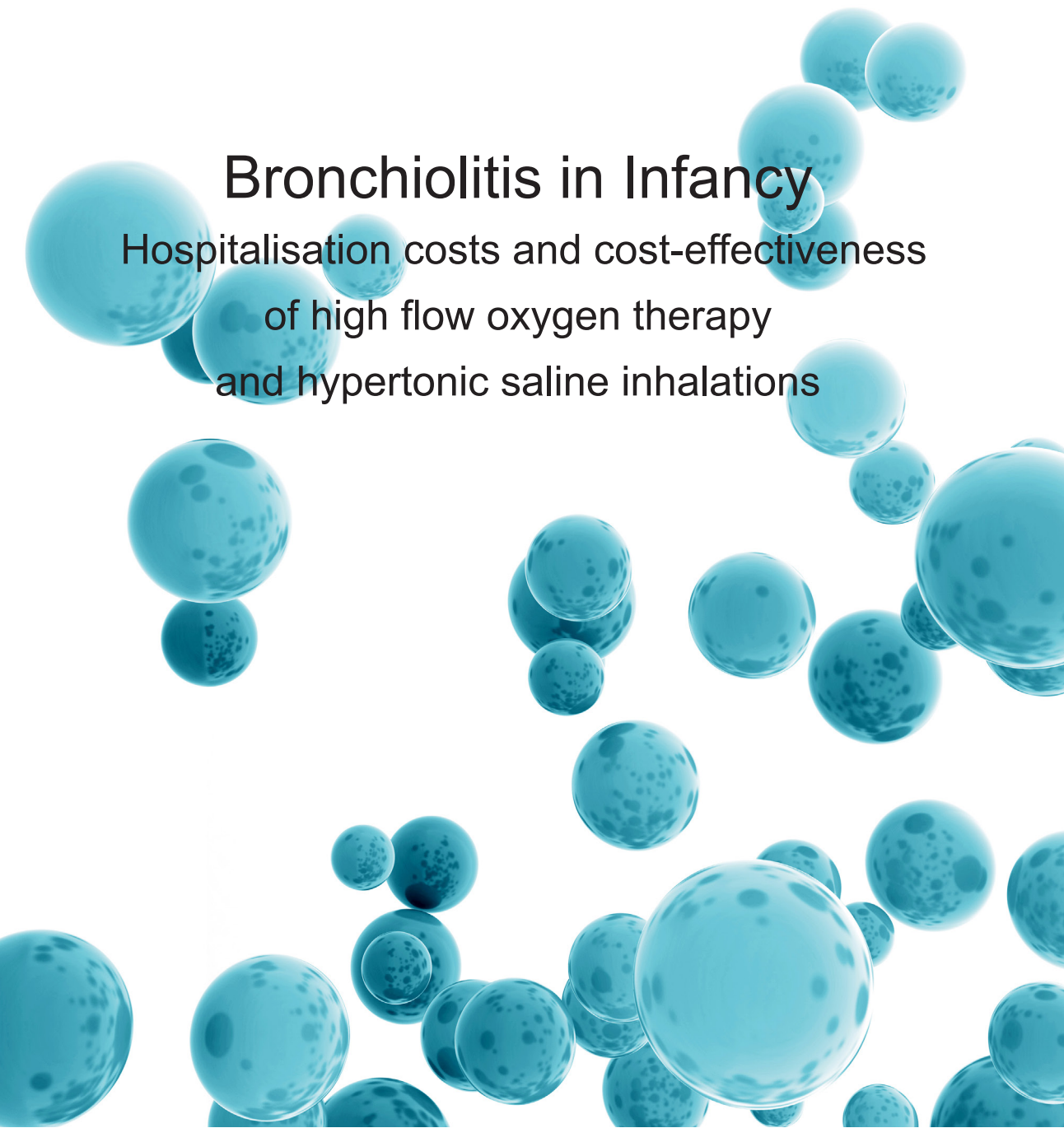# PAULA HEIKKILÄ

# Bronchiolitis in Infancy

Hospitalisation costs and cost-effectiveness
of high flow oxygen therapy
and hypertonic saline inhalations

PAULA HEIKKILÄ

# Bronchiolitis in Infancy

## Hospitalisation costs and cost-effectiveness of high flow oxygen therapy and hypertonic saline inhalations

■

PAULA HEIKKILÄ

# Bronchiolitis in Infancy

Hospitalisation costs and cost-effectiveness
of high flow oxygen therapy
and hypertonic saline inhalations

# UNIVERSITY OF TAMPERE

The originality of this thesis has been checked using the Turnitin OriginalityCheck service in accordance with the quality management system of the University of Tampere.

Cover design by
Mikko Reinikka

*To my loving family*

# ABSTRACT

**Background:** Bronchiolitis is the most common infectious reason for hospitalisation in infancy. Morbidity is high, and approximately 1% to 3% of infants under 12 months of age are hospitalised annually. As demonstrated in two Finnish studies, 6% of those hospitalised are treated in the paediatric intensive care unit (PICU). The hospitalisation costs are high in all countries and are increasing. The treatment of bronchiolitis is supportive. Hypertonic saline (HS) inhalations have been widely used in recent years, and high flow oxygen therapy (HFOT) is a promising new treatment method.

The aim of this thesis is to evaluate the hospitalisation costs of bronchiolitis in Finland. Additionally, the cost-effectiveness of HFOT compared to standard low flow oxygen therapy (LFOT) is evaluated, as well as the effectiveness and cost-effectiveness of HS inhalations compared to normal saline (NS) inhalations, or to standard treatment without inhalations.

**Materials and methods:** The cost analysis was done in form of a case-control study. We collected the medical data and hospitalisation costs for all infants with bronchiolitis treated in the PICU (n=80) of the Tampere University Hospital between the years 2000 and 2012. As controls (n=160), we collected the data of infants with bronchiolitis treated in the emergency department just before, and one just after, the index case. The hospitalisation costs were based on municipal billing, and the viewpoint was that of the health care providers. For evaluation of cost-effectiveness we used the cost data collected in this study, and the data for evaluating the effectiveness of HFOT and HS inhalations were obtained from previously published studies. The cost-effectiveness analyses were carried out by decision tree models that compared HFOT to LFOT, as well as HS to NS. Additionally, the effectiveness of HS inhalations was evaluated by meta-analysis.

**Results:** The direct total mean hospitalisation costs of bronchiolitis were €8,061 for those who were treated in the PICU, €1,834 for those treated on the ward, and €359 for those treated in the emergency department only. The higher costs were correlated to a longer length of stay in the hospital, especially in the PICU.

Additionally, lower gestational age and age on admission were weakly linked to the higher costs. Other factors strongly associated with higher costs were not found. HFOT was both more effective and less expensive when compared to LFOT. The expected hospitalisation costs were between €1,312 and €2,644 for HFOT, and between €1,598 and €3,764 for LFOT. HFOT was the dominant treatment in all models in comparison to LFOT. HS inhalations were slightly less expensive than control treatments, but the effectiveness was low and, in some situations, even absent. The effectiveness of HS inhalations compared to controls decreased by the publication time of this study. Cumulative mean difference of the length of stay in the hospital was nearly 12 hours, and the cumulative risk ratio for hospitalisation was 0.771, favouring HS inhalations.

**Conclusion:** The hospitalisation costs of infant bronchiolitis are four times higher if intensive care is needed when compared to ward treatment, and over 20 times higher when compared to the treatment in the emergency department. HFOT seems to decrease the use of intensive care, and further to decrease, the hospitalisation costs. However, the results based on the theoretical model with historical controls used here need to be confirmed by prospective randomised controlled trials. On the other hand, HS inhalations are not effective enough for any real cost-saving to be gained, and such inhalations should not be routinely used in the treatment of infant bronchiolitis.

# TIIVISTELMÄ

**Tausta:** Bronkioliitti eli ilmatiehyttulehdus on yleisin sairaalahoidon syy alle vuoden ikäisillä vauvoilla. Sairastuvuus bronkioliittiin on korkeaa ja 1-3 % tästä ikäryhmästä hoidetaankin vuosittain sairaalassa bronkioliitin vuoksi. Suomalaisissa tutkimuksissa on havaittu, että noin 6 % sairaalahoidetuista vauvoista päätyy tehohoitoon. Tutkimusten mukaan sairaalahoidon kustannukset ovat nousseet eri maissa. Bronkioliitin sairaalahoito perustuu oireiden helpottamiseen; hypertonisia keittosuolaliuosinhalaatioita on käytetty laajasti viime vuosina ja korkeavirtaushappihoito on uusi, lupaava hoitomuoto.

Tämän väitöstutkimuksen tavoitteena on arvioida sairaalahoidon kustannuksia Suomessa. Lisäksi verrataan korkeavirtaushappihoidon ja perinteisen lisähappihoidon kustannusvaikuttavuutta, kuten myös hypertonisten ja normaalien keittosuolaliuosinhalaatioiden vaikuttavuutta ja kustannusvaikuttavuutta.

**Aineisto ja menetelmät:** Kustannusanalyysi on tehty tapaus-verrokki asetelmasta. Potilasaineisto koostuu kaikista vauvoista (n=80), jotka ovat olleet tehohoidossa bronkioliitin takia vuosien 2000–2012 välillä Tampereen yliopistollisessa sairaalassa. Verrokkipotilaiksi (n=160) valittiin ne vauvat, jotka ovat saapuneet päivystyspoliklinikalle hoitoon bronkioliitin takia juuri ennen tehohoidettua vauvaa ja heti tämän jälkeen. Kustannustiedot koostuvat kuntalaskutustiedoista, joten työn näkökulma on rajattu terveydenhuollon palveluntarjoajan näkökulmaan. Kustannusvaikuttavuusanalyyseissä käytettiin omasta aineistosta saatavia kustannustietoja ja vaikuttavuustiedot koottiin aiemmin julkaistuista tutkimuksista. Kustannusvaikuttavuusanalyysit olivat mallintavia päätösanalyyseja, joissa käytettiin analyysimenetelminä päätöspuita ja näissä ensiommäisessä verrattiin korkeavirtaushappihoitoa perinteiseen lisähapenantoon ja toisessa hypertonisia keittosuolaliuosinhalaatioita normaaleihin keittosuolaliuosinhalaatioihin. Lisäksi keittosuolaliuosinhalaatioiden vaikuttavuutta arvioitiin meta-analyysin avulla.

**Tulokset:** Bronkioliitin suorat, keskimääräiset sairaalahoidon kustannukset olivat 8 061€, kun hoitoon liittyi tehohoitojakso, 1 834€, kun hoito oli toteutettu

vuodeosastolla ja 359€, kun hoitoa oli annettu vain sairaalan päivystyspoliklinikalla. Korkeammat kustannukset olivat voimakkaasti yhteydessä pidempään sairaalahoidon kestoon ja erityisesti pidempään tehohoidon kestoon. Heikompi yhteys havaittiin ennenaikaisuuden ja nuoremman iän suhteen. Muita korkeisiin kustannuksiin voimakkaasti yhteydessä olevia tekijöitä ei havaittu. Korkeavirtaushappihoito oli vaikuttavampaa ja edullisempaa perinteiseen lisähapen antoon verrattuna. Odotetut sairaalahoidon kustannukset vaihtelivat korkeavirtaushappihoidon ryhmässä 1 312€ ja 2 644€ välillä ja perinteisen lisähappihoidon ryhmässä 1 598€ ja 3 764€ välillä. Korkeavirtaushappihoito oli dominoiva hoitomuoto perinteiseen lisähapenantoon verrattuna huolimatta siitä, mitä mallia analyyseissa käytettiin. Hypertoniset keittosuolaliuosinhalaatiot olivat vain hieman edullisempia verrattuna kontrollihoitoon, mutta niiden vaikuttavuus oli matalaa ja tietyissä tilanteissa jopa olematonta. Uudemmat, vuoden 2012 jälkeen julkaistut tutkimukset eivät enää osoita vastaavaa vaikuttavuutta. Hypertonisia keittosuolaliuosinhalaatioita vuodeosastolla saaneilla keskimääräinen sairaalahoidon kesto oli liki 12 tuntia vähemmän kuin kontrollihoidetuilla. Poliklinikkahoidossa kumulatiivinen riskisuhde sairaalahoidolle oli 0.72 suosien hypertonisia keittosuolaliuosinhalaatioita.

**Johtopäätökset:** Sairaalahoidon kustannukset ovat tehohoidetuilla neljä kertaa korkeammat kuin osastohoidetuilla ja jopa 20 kertaa korkeammat kuin polikliinisesti hoidetuilla. Korkeavirtaushappihoito näyttää vähentävän tehohoidon käyttöä ja sen myötä sairaalahoidon kustannuksia. Tämä tulos perustuu kuitenkin mallintavaan tutkimukseen ja se pitää varmistaa prospektiivisilla satunnaistetuilla ja kontrolloiduilla tutkimuksilla. Hypertoniset keittosuolaliuosinhalaatiot eivät puolestaan vaikuta olevan niin tehokkaita, että niiden käytöllä voisi syntyä todellista kustannusten säästöä sairaalahoidossa. Tämän takia niitä ei enää pitäisi käyttää rutiinisti bronkioliitin hoidossa.

# CONTENTS

# LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications, which will be referred to throughout by the numerals I-IV:

I       Heikkilä P, Forma L, Korppi M. Hospitalisation costs for infant bronchiolitis are up to 20 times higher if intensive care is needed. *Acta Paediatr. 2015;104:269-273.*

II      Heikkilä P, Forma L, Korppi M. High-flow oxygen therapy is more cost-effective for bronchiolitis than standard treatment - a decision-tree analysis. *Pediatr Pulmonol. 2016;51:1393-1402.*

        Heikkilä P, Forma L, Korppi M. Erratum: High-flow oxygen therapy is more cost-effective for bronchiolitis than standard treatment - A decision-tree analysis. *Pediatr Pulmonol. 2017 DOI:10.1002/ppul.23660*

III     Heikkilä P, Mecklin M, Korppi M. The cost-effectiveness of hypertonic saline inhalations for infant bronchiolitis: a decision analysis. *World Journal of Pediatrics, in press.*

IV      Heikkilä P, Renko M, Korppi M. Hypertonic saline inhalations in infant bronchiolitis – a cumulative meta-analysis. *August 2017 (Submitted).*

# ABBREVIATIONS

| | |
|---|---|
| AAP | American Academy of Pediatrics |
| BPD | Bronchopulmonary dysplasia |
| C | Costs |
| CEA | Cost-effectiveness analysis |
| CPAP | Continued positive air pressure |
| E | Effectiveness |
| ED | Emergency department |
| HFOT | High flow oxygen therapy |
| HS | Hypertonic (≥3%) saline |
| ICER | Incremental cost-effectiveness ratio |
| LFOT | Low flow oxygen therapy |
| LOS | Length of stay |
| LRTI | Lower respiratory tract infection |
| MD | Mean difference |
| MV | Mechanical ventilation |
| NS | Normal (0.9%) saline |
| OECD | Organisation for Economic Co-operation and Development |
| OR | Odds ratio |
| PICU | Paediatric intensive care unit |
| RCT | Randomised controlled trial |
| RR | Risk ratio |
| RSV | Respiratory syncytial virus |
| UK | United Kingdom |
| USA | United States of America |

# 1   INTRODUCTION

Bronchiolitis is defined as the first breathing difficulty in an infant under 12 months of age that is associated with an acute lower respiratory tract infection (LRTI) (Meissner 2016). The causative agent for bronchiolitis is a virus, and the major one is the respiratory syncytial virus (RSV) (Florin, Plint, Zorc 2016). The diagnosis of bronchiolitis is clinical and based on typical signs and symptoms. Bronchiolitis starts with symptoms of an upper respiratory infection and progresses within a few days to an LRTI with symptoms such as coughing, expiratory breathing difficulty, increased work of breathing and tachypnoea (Florin, Plint, Zorc 2016).

Bronchiolitis is a significant public health problem in infancy; the morbidity is high and the costs substantial. Globally, RSV was associated with 33.8 million episodes of LRTI, and with approximately 3.4 million hospitalised episodes of LRTI in children less than five years old (Nair et al. 2010). For infants under 12 months of age, the annual incidence of bronchiolitis or bronchitis caused by RSV was 75/1000 in general practices and 37.6/1000 in hospitals, and age-specific mortality was 0.08/1000 in the UK, as reported in a population-based study (Taylor et al. 2016). In general, 1% to 3% of all infants are hospitalised because of bronchiolitis (Smyth and Openshaw 2006; Zorc and Hall 2010), and 5% to 6% of hospitalised infants are treated in the paediatric intensive care unit (PICU) (Hasegawa et al. 2014; Jartti et al. 2014). In Finland, within the population of 55,472 new-borns in 2015 (Statistics 2016), can be estimated that 554 to 1,664 infants are hospitalised annually because of bronchiolitis depending on the extent of the epidemic during year. The annual incidence of bronchiolitis in infants less than six months of age that were admitted to the emergency department (ED) was 37/1000, and 26/1000 were hospitalised according to a Finnish study (Pruikkonen et al. 2014).

The total national hospitalisation costs incurred by bronchiolitis were reported to be as high as $1.73 billion USD annually from the viewpoint of care holder in the USA (Hasegawa et al. 2013a). In a Spanish study, the annual costs of bronchiolitis for society were €20 million for ED treatment (Garcia-Marcos et al.

2014). Furthermore, health care use and costs were higher for those infants with bronchiolitis than for those without during the first year of life (Roggeri et al. 2016; Shi et al. 2011).

Majority of bronchiolitis patients are under six months of age and, at that age, most patients are treated in the hospital. If an infant´s general condition is poor, work of breathing is increased, oxygen saturation is decreased or fluid intake is insufficient, the infant should be admitted to the hospital (Ricci et al. 2015; Tapiainen et al. 2016). In the hospital, supportive therapy with the principle of minimal handling may be the optimal approach (Meissner 2016). The infant´s breathing work and oxygen saturation are monitored and treated if needed, and nutrition and hydration are guaranteed (Florin, Plint, Zorc 2016; Meissner 2016). Medicaments, such as antibiotics, beta-agonists, racemic adrenaline or corticosteroids, are neither effective nor recommended (Farley et al. 2014; Fernandes et al. 2013; Gadomski and Brower 2010; Hartling et al. 2011).

High flow oxygen therapy (HFOT) has become a promising new way to treat respiratory distress in infant bronchiolitis. In HFOT heated, humidified and blended air-oxygen mixture is delivered via the nasal cannula (Mikalsen, Davis, Oymar 2016). The flow rate of 2L/min to 8L/min produces sufficient nasopharyngeal pressure and end-expiratory lung volume in descriptive studies. Additionally, the use of HFOT seems to reduce work of breath, respiratory rate and heart rate, and to improve oxygen saturation (Arora et al. 2012; Bressan et al. 2013; Hilliard et al. 2012; Hough, Pham, Schibler 2014; Kelly, Simon, Sturm 2013; Mayfield et al. 2014). HFOT seems to be well tolerated and safe for infants with bronchiolitis, but its effectiveness is still tentative (Sinha et al. 2015), and hence further, preferably large, randomised controlled trials (RCT) are needed.

Hypertonic saline (HS) inhalations affect, in theory, decreasing sub-mucosal oedema in the respiratory epithelium via osmosis, and improving mucus clearance by rehydration (Canty and Colomb-Lippa 2014; Mandelberg and Amirav 2010a). HS inhalations have been used and their effectiveness has been studied in relation to bronchiolitis since 2003. The latest Cochrane review included 11 studies and 1,090 infants with bronchiolitis, and compared HS inhalations to normal saline (NS) inhalations. This 2013 Cochrane review results showed that HS inhalations decreased the length of stay (LOS) in the hospital. The mean difference (MD) was -1.15 days (95% Confidence Interval, CI, -1.49 to -0.82), and clinical severity score decreased during the first three days when HS was used in the hospital. The hospital admission rate decreased (risk ratio, RR, 0.63, 95%CI 0.37 to 1.07), but this decrease was statistically insignificant, when HS was used in the ED (Zhang

et al. 2013). Nevertheless, the results of the recent RCTs and meta-analyses did not favour HS unambiguously anymore and, mostly, the results have even been negative (Brooks, Harrison, Ralston 2016; Everard et al. 2014; Flores, Mendes, Neto 2016; Overmann and Florin 2016; Wu et al. 2014).

The cost-effectiveness of HFOT compared to low flow oxygen therapy (LFOT), or that of HS inhalations compared to NS inhalations, has not yet been studied. Nowadays, even the effectiveness of HS inhalations is debated. Therefore, more evidence is needed about the effectiveness and cost-effectiveness of both HFOT and HS inhalations.

The aim of this thesis is to evaluate the hospitalisation costs of bronchiolitis in the Tampere University Hospital from the viewpoint of the care holder. These costs are then used to analyse the cost-effectiveness of HFOT in comparison to LFOT, as well as the cost-effectiveness of HS inhalations in comparison to NS inhalations, or to standard care without inhalation. Lastly, the effectiveness of HS inhalations is compared to NS inhalations, or to standard care, by cumulative meta-analysis. The target is to give information to assist decision making when choosing between alternative modalities that can be used in infant bronchiolitis treatment in hospitals.

# 2   REVIEW OF THE LITERATURE

## 2.1   Bronchiolitis

### 2.1.1   Bronchiolitis definition

Bronchiolitis is an acute lower respiratory tract infection (LRTI) usually caused by a virus. Breathing difficulty, with or without wheezing, is part of this illness (Zorc and Hall 2010). However, the upper age limit set for defining bronchiolitis is controversial. In Europe, bronchiolitis is usually defined as the first episode of expiratory breathing difficulty in infants younger than 12 months of age (Mecklin et al. 2014; Meissner 2016). In the USA, the upper age limit of bronchiolitis is 24 months (Ralston et al. 2014). In the national health guidelines in the UK, bronchiolitis is defined as an illness that occurs under 24 months of age, but usually under 12 months of age, peaking at three to six months (National Collaborating Centre for Women's and Children's Health (UK) 2015). In some articles, even six months was suggested as the upper age limit (Korppi, Koponen, Nuolivirta 2012; Korppi 2015; Pruikkonen et al. 2014). In this thesis, bronchiolitis is defined as a viral LRTI with breathing difficulty in infants younger than 12 months.

The diagnosis of bronchiolitis is clinical, based on typical signs and symptoms. Commonly, bronchiolitis begins with symptoms of an upper respiratory tract infection, such as nasal congestion and rhinorrhoea (Meissner 2016).  After a few days, infection results in extensive inflammation of the bronchiolar epithelium, oedema of the submucosa, increased mucus production and necrosis of epithelial cells (Florin, Plint, Zorc 2016; Zorc and Hall 2010). The symptoms worsen during the first five days following the disease onset (Pruikkonen et al. 2014). Anatomic factors, such as the development of alveoli in number and function and the development of respiratory muscle fibres, at least partly cause susceptibility to respiratory failure in infants (Sinha et al. 2015). Furthermore, cough, tachypnoea, chest retractions, increased respiratory rate, inspiratory crackles or expiratory wheezing, and sometimes cyanosis, high fever and poor general appearance, are

all symptoms associated with bronchiolitis (Meissner 2016; National Collaborating Centre for Women's and Children's Health (UK) 2015).


## 2.1.2 Epidemiology

Respiratory syncytial virus (RSV) is the most common agent in infant bronchiolitis. In the Finnish prospective cohort study with 408 infants under 24 months of age, 43% of bronchiolitis patients were infected by RSV, 32% by rhinovirus and 7% by metapneumovirus (Jartti et al. 2014). Other prospective studies from Italy, USA and Norway in infants under 12 months of age with bronchiolitis, showed that 60% to 83% of patients were infected by RSV, 11% to 34% by rhinovirus, and 10% to 61% had multiple infections caused by two or more viruses (Cangiano et al. 2016; Miller et al. 2013; Skjerven et al. 2016). Other viruses that caused bronchiolitis were the human bocavirus, coronavirus, influenza and parainfluenza viruses (Cangiano et al. 2016; De Paulis et al. 2011; Jartti et al. 2014; Miller et al. 2013).

The peak incidence of bronchiolitis, as well as the RSV infection, is in the winter months (Cangiano et al. 2016; Carroll et al. 2008; Hervas et al. 2012; Hogan et al. 2016; Panozzo, Fowlkes, Anderson 2007). In a laboratory-based surveillance from the USA, the duration of the RSV infection season varied on average between 13 and 16 weeks (Panozzo, Fowlkes, Anderson 2007). In Finland, the seasonality of laboratory-confirmed and registered RSV infections in children under five years of age conforms to the outbreak seasons reported by other countries around the world. The RSV infection peaks are in the winter months with approximately two to four months duration (Figure 1). Figure 1 demonstrates annual variations of RSV infections, and shows that every other year the peak is higher.

**Figure 1.** The number of RSV infections in children between zero and four years old in Finland, monthly, between 2000 and 2015 (National Institute of Health and Welfare, Finland 2016).

A population-based, retrospective cohort study from the USA, found that the bronchiolitis incidence rate increased 41% over a nine-year study period. On average, for every 1000 infants under 12 months of age, there were 238 outpatient visits, 77 emergency department visits and 71 hospitalisations annually during the study period (Carroll et al. 2008). Another cross-sectional study from the USA, found that the hospitalisation rate decreased from 17.9/1000 person-years in 2000 to 14.9/1000 person-years in 2009 among all American children under 24 months of age. Nevertheless, bronchiolitis accounted for 18.1% of all hospitalisations in infants under 12 months old (Hasegawa et al. 2013b). Furthermore, hospitalisation rates vary between the countries. In the birth cohort from the UK the hospitalisation rate for infants under 12 months of age was 24.1/1000 (Murray et al. 2014) compared to 54/1000 in the Italian birth cohort (Lanari et al. 2015) and to 41.4/1000 in the retrospective register-based study from Spain (Gil-Prieto et al. 2015), or to 26.3/1000 in the French birth cohort (Iacobelli et al. 2017).

Bronchiolitis is the most common reason for intensive care in infancy (Oymar, Skjerven, Mikalsen 2014). Bronchiolitis is also the reason for the average 11.8% of all paediatric intensive care unit (PICU) admissions in infants under 12 months of age in the UK (Green et al. 2016). One prospective and one retrospective study from Finland found that 6.3% (Jartti et al. 2014) and 6.1% (Pruikkonen et al. 2014) of all hospitalised infants with bronchiolitis, respectively, were treated in the PICU. Other reported PICU admission rates were up to 16% (Hasegawa et al. 2015) in the USA, and even up to 23% (Perez-Yarza et al. 2015) in Spain. In

industrialised countries, the mortality rate for bronchiolitis is low, approximately 0.15% (Gil-Prieto et al. 2015) to 0.8% (Hervas et al. 2012).

The length of stay (LOS) in hospital varied across the countries. In Finland, the median LOS was two days in a prospective study (Jartti et al. 2014) and 2.2 days in a retrospective study (Pruikkonen et al. 2014). In other countries, the median LOS was one day in the UK (Murray et al. 2014) and three days in the USA (Hasegawa et al. 2014). In Spain, the median LOS was higher, six days for RSV bronchiolitis and five days for non-RSV bronchiolitis (Hervas et al. 2012). Additionally, some other studies have documented that RSV aetiology was associated with longer LOS (Jartti et al. 2014; Skjerven et al. 2016).

## 2.1.3    Risk factors and prevention

Young age, male gender, low birth weight and preterm birth are some factors that increase the risk of bronchiolitis (Carroll et al. 2008; Meissner 2016). Young age of mothers, presence and number of siblings, day care attendance and lack of breastfeeding are family-related risk factors for bronchiolitis (Carroll et al. 2008; Perez-Yarza et al. 2015). The infant's exposure to tobacco smoke during pregnancy and/or infancy increases the risk of bronchiolitis, and the risk increases linearly in relation to the amount of exposure (Carroll et al. 2008).

Additionally, hemodynamically significant congenital heart diseases and chronic lung diseases, especially bronchopulmonary dysplasia (BPD) increase the risk of bronchiolitis (Meissner 2016; Murray et al. 2014), as well as Down´s syndrome, cerebral palsy and other nervous system congenital abnormalities (Murray et al. 2014). Furthermore, risk factors for PICU treatment are younger age (under six months), preterm birth and BPD, as well as certain clinical signs on admission, such as high respiratory rate or presence of atelectasis (Hasegawa et al. 2015; Hervas et al. 2012).

The easiest and cheapest ways of preventing respiratory infections like bronchiolitis are hand disinfection and a soap and water wash during the epidemic season. Breast feeding and stopping tobacco smoking are recommended, not only to prevent bronchiolitis, but for many other reasons. (Ralston et al. 2014) The development of a vaccine against RSV has not yet been successful. However, passive immunisation with palivizumab, the humanised mouse monoclonal antibody, is available. Palivizumab prophylaxis is shown to be effective in reducing hospitalisation when given monthly to infants with high risk of an RSV

infection (Andabaka et al. 2013; Drysdale, Green, Sande 2016; Wang, Bayliss, Meads 2011).

The American Academy of Pediatrics (AAP) recommends palivizumab injections to infants with hemodynamically significant heart disease or chronic lung disease, and to preterm infants born at under 32 weeks of gestation. The injections need to be given up to five times to cover the entire RSV epidemic duration (Ralston et al. 2014). An effectiveness study in the USA showed that the hospitalisation rate for infant bronchiolitis did not change significantly, being 5.37/1000 children before the implementation of the AAP recommendation, versus 5.78/1000 children after. Instead, following the recommendation the use of palivizumab injections decreased from 21.7 doses/1000 children to 10.3 doses/1000 children under 24 months of age. (Grindeland et al. 2016)

Palivizumab is an expensive prophylaxis (Drysdale, Green, Sande 2016) and the economic evaluations of palivizumab prophylaxis have given inconsistent results (Andabaka et al. 2013). The evaluation of cost-effectiveness varied from very cost-effective to not cost-effective between studies. That variation probably resulted from the difference in the willingness-to-pay threshold used, and the resources taken into account in the studies (Andabaka et al. 2013).

### 2.1.4    Summary of definition, epidemic and risk factors of bronchiolitis

Bronchiolitis is defined as the first breathing difficulty in an infant under 12 months of age with a viral acute LRTI. The main causative agent is RSV, and the peaks of annual epidemics take place during the winter months. Approximately 2% to 3% of infants are hospitalised in their first year of life because of bronchiolitis. The risk factors for bronchiolitis are young age at the time of an epidemic, preterm birth, male gender, as well as congenital heart diseases and chronic lung diseases, especially BPD. Only infants with very preterm birth (<32 weeks) benefit from passive immunisation using prophylaxis against bronchiolitis.

## 2.2    Treatment of bronchiolitis

### 2.2.1    Supportive treatment

Most infants with bronchiolitis are treated in the hospital. Infants should be admitted to the hospital when oxygen saturation is less than 92% when measured by pulse oximetry, breathing work is increased as shown through an assessment of tachypnoea and chest indrawing, the infant exhibits instances of apnoea, or its oral fluid intake is insufficient (Ricci et al. 2015; Tapiainen et al. 2016). However, the best treatment practice for bronchiolitis patients is still under debate, because of a lack of curative therapy (Meissner 2016). The current recommendation is that the infants hospitalised for bronchiolitis are treated with supportive therapy, applying the principle of "minimal handling".

Oxygen saturation and breathing work in infants should be monitored. Nowadays, intermittent, but regular, oxygen saturation checks are more often recommended than continuous monitoring, if oxygen support is not needed (Florin, Plint, Zorc 2016). The sufficient level of saturation varies from 90% to 92% (Ralston et al. 2014; Ricci et al. 2015). Two randomised studies from Canada (Schuh et al. 2014) and the UK (Cunningham et al. 2015b) evaluated the sufficient level of saturation for infants with bronchiolitis by masking the oximetry to show three-point (Canada) or four-point (UK) higher values than true values. Infants monitored with manipulated oximetry in the Canadian study were less likely to be admitted to the hospital within 72 hours (41% vs 25%; OR 2.1, 95%CI 1.2 to 3.8) than those monitored with standard oximetry (Schuh et al. 2014). In the UK, when manipulated oximetry was used on the ward it was found that those infants monitored with it were discharged earlier (median LOS in hospital was 40.9 hours, interquartile range [IQR] 21.8 to 67.3 vs 50.9 hours, IQR 23.1 to 93.4), and were treated with supplement oxygen for shorter durations than those monitored with standard oximetry (Cunningham et al. 2015b). Adverse events were recorded in both groups, but there were no significant differences between the groups in terms of the type and severity of events (Cunningham et al. 2015b).

Nutrition and hydration constitute an important part of bronchiolitis therapy. If feeding is insufficient, nasogastric and orogastric tubes or isotonic intravenous fluids are recommended, with some differences between the guidelines (Florin, Plint, Zorc 2016). Traditionally, intravenous fluid supplementation has been used in many countries. Intravenous fluids can decrease aspiration risks, and do not affect the breathing. Problems with intravenous fluids are a lower calorie intake

and a higher risk of over-hydration and electrolyte imbalance (Oymar, Skjerven, Mikalsen 2014). Some guidelines recommend delivery of fluids via naso- or orogastric tubes over intravenous fluids administration (Florin, Plint, Zorc 2016), because enteral hydration attains a better nutritional status (Oymar, Skjerven, Mikalsen 2014). A recent retrospective study did not find significant differences in adverse events between the groups treated with either nasogastric tube or intravenous fluid administration (Oakley et al. 2016). Still, there is not enough evidence either for or against enteral or parenteral fluid supplementation (Florin, Plint, Zorc 2016; Oymar, Skjerven, Mikalsen 2014).

Nasal suctioning may be helpful for clearing the nares, improving the work of breathing, and further improving feeding. On the other hand, it may irritate the nasal mucosa and cause oedema. There are no good studies done about the benefits of suctioning and, for that reason, it cannot be recommended for routine use (Florin, Plint, Zorc 2016).

Medicaments, such as antibiotics, antiviral agents, beta-agonists, inhaled racemic adrenalin and inhaled or systemic corticosteroids, are neither effective nor recommended for bronchiolitis treatment (Farley et al. 2014; Fernandes et al. 2013; Florin, Plint, Zorc 2016; Gadomski and Brower 2010; Hartling et al. 2011; Skjerven et al. 2015). Nevertheless, on-demand inhaled racemic adrenalin or beta-agonist may be given to selected infants, but the treatment can be continued only if it is shown to improve symptoms through careful monitoring (Florin, Plint, Zorc 2016; Skjerven et al. 2013).

Furthermore, chest physiotherapy is not recommended (Roque i Figuls et al. 2016). Chest radiology, viral or bacterial testing, and blood gas measurements are not routinely recommended, but could be an option when intensive care is considered (Florin, Plint, Zorc 2016).

```
┌─────────────────────────────────────────────────────────────────────────┐
│ Infant with signs or symptoms of bronchiolitis, with or without respiratory difficulty │
└─────────────────────────────────────────────────────────────────────────┘
                                    │
                                    ▼
┌─────────────────────────────────────────────────────────────────────────┐
│ Parents are worried and go to see the doctor;                             │
│ the doctor at the outpatient clinic decides to admit the infant to the hospital │
└─────────────────────────────────────────────────────────────────────────┘
         │                                              │
         ▼                                              ▼
┌──────────────────────────────┐        ┌──────────────────────────────────┐
│ On the ward:                 │        │ In the PICU:                     │
│ * monitoring the breathing work and oxygen │◄──────►│ * taking care of vitals,    │
│ saturation, supplementary oxygen given if  │        │ CPAP, even providing mechanical ventilation │
│ needed                       │        │ if needed                        │
│ * taking care of nutrition and hydration │       │ * taking care of nutrition and hydration, │
│ * laboratory and radiology studies minimised │    │ feeding via nasogastric tube or intravenously │
│                              │        │ if needed                        │
│                              │        │ * laboratory and radiology studies upon │
│                              │        │ clinical indications avoiding routines │
└──────────────────────────────┘        └──────────────────────────────────┘
         │                                              │
         ▼                                              ▼
┌─────────────────────────────────────────────────────────────────────────┐
│ Departure home: Breathing work is normal, no supplementary oxygen is needed and fluid intake is │
│ adequate                                                                  │
└─────────────────────────────────────────────────────────────────────────┘
```

**Figure 2.** The treatment path of an infant treated for bronchiolitis in a hospital (literature summary).

To summarise, successful treatment of infants with bronchiolitis is based on careful clinical observations; supplemental oxygen and non-invasive or even invasive ventilation support are given if needed, and nutrition and hydration are guaranteed by nasogastric or intravenous fluid administration if needed (Figure 2). Otherwise treatment is based on what is known as "minimal handling", meaning that infants can sleep without interruptions.

### 2.2.2    Hypertonic saline inhalations

Due to promising results that hypertonic saline (HS) inhalations have shown in cystic fibrosis, many trials have been done on HS inhalations for the treatment of infant bronchiolitis. Bronchiolitis causes, as mentioned above, epithelial cell necrosis, sub-mucosal oedema, increased mucus production and dehydration of airway surface liquid. Inhaling HS affects the respiratory epithelium by osmosis. Theoretically, inhaling HS rehydrates the respiratory epithelium, decreases oedema, increases mucus viscosity, restores ciliary function and, finally, improves mucus clearance (Canty and Colomb-Lippa 2014; Mandelberg and Amirav 2010a). In a mice study, however, rehydration with HS only reduced

obstruction, without having any substantial effect on inflammation (Graeber et al. 2013).

Since 2003, the effectiveness of HS inhalations in bronchiolitis treatment has been studied widely. There are over 20 prospective RCTs, performed in different countries around the world. Most studies compared 3%, 5% or 7% HS, with or without a bronchodilator, to 0.9% NS inhalations, again with or without bronchodilators. Because of the large number of studies with conflicting results, the review of the results is limited to those included in the recent meta-analyses and systemic reviews only.

The latest Cochrane review that includes 11 studies and 1,090 infants with bronchiolitis was published in 2013. HS inhalations seemed to decrease the LOS in hospital (MD, -1.15 days, 95%CI -1.49 to -0.82), and the clinical severity score during the first three days in the hospital, when compared to NS inhalations. In addition, the admission rate decreased (RR, 0.63, 95%CI 0.37 to 1.07) when HS inhalation were given for bronchiolitis in the ED, but this decrease was not statistically significant (Zhang et al. 2013). The studies published after the 2013 Cochrane review have reported mainly negative results (Everard et al. 2014; Flores, Mendes, Neto 2016; Teunissen et al. 2014; Wu et al. 2014).

In 2015, the authors of the 2013 Cochrane review published a systematic review and meta-analysis. Their meta-analysis included 24 studies and 3,209 infants with bronchiolitis: 15 studies for inpatient analysis and seven for outpatient analysis. The LOS was still lower (MD -0.45 days, 95%CI -0.82 to -0.08), as was the average clinical severity score in the first three days, when HS inhalations were compared to NS inhalations. HS inhalations also decreased the admission rate (RR 0.80, 95%CI 0.67 to 0.96) when given to outpatients in the ED. (Zhang et al. 2015) In the same year (2015), another systematic review and meta-analysis, including 15 studies and 1,922 infants with bronchiolitis, were also published. In this meta-analysis, HS inhalations decreased the LOS to a lesser extent (MD, -0.36, 95%CI -0.50 to -0.22), but still significantly in comparison to NS inhalations. This meta-analysis reported only one possible severe adverse event connected to HS inhalations. (Maguire et al. 2015)

In the meta-analyses presented above, the heterogeneity between the studies measured by the Higgins´ I² test were considerable in the inpatient analyses, but low in the outpatient analyses. The two most recently published meta-analyses addressed that problem. In the first of them, 24 studies and 3,209 infants with bronchiolitis were included, and subgroup analyses were done both for studies with a high or unclear risk of bias, and for studies with a low risk of bias,

respectively. In the analysis that included studies with a high or unclear risk of bias, the MD of the LOS decrease was -0.65 days (95%CI -1.14 to -0.15), and in the analysis including only studies with a low risk of bias it was -0.26 days (95%CI -0.82 to 0.30). (Overmann and Florin 2016) Thus, the difference was not statistically significant anymore. The second meta-analysis done included 18 studies and 2,063 infants with bronchiolitis. When heterogeneity was under control, the mean difference of the LOS lost the statistical significance and even changed the direction with the final influence being +0.02 days (95%CI -0.14 to +0.17). (Brooks, Harrison, Ralston 2016)

To summarise these results, while HS inhalations may slightly decrease the LOS, such improvement decreases over time. The latest results, as well as the meta-analyses that have tried to monitor the heterogeneity of the included studies, do not support the use of HS for inpatient treatment anymore. HS inhalations may be useful for outpatient treatment, however, the evidence is still insufficient for any routine use or recommendations.


## 2.2.3    High flow oxygen therapy

High flow oxygen therapy (HFOT), also called high flow nasal cannula (HFNC) therapy, has become a promising new option for bronchiolitis treatment. In HFNC therapy, heated, humidified and blended air-oxygen mixture is delivered via the nasal cannula with a flow rate of 2L/min or more (Mikalsen, Davis, Oymar 2016). The term HFOT is used as a synonym for HFNC in this thesis.

HFOT was first applied on a large scale as an alternative to continuous positive airway pressure (CPAP) used with preterm infants with apnoea. Subsequently, it became rapidly popular, not only in neonatology, but also in paediatrics for the management of acute respiratory distress in both infants and children (Haq et al. 2014; Hutchings, Hilliard, Davis 2015; Kotecha et al. 2015). HFOT seems to be well tolerated by infants, children and adults with respiratory distress (Mikalsen, Davis, Oymar 2016). A meta-analysis, which included nine studies and 1,112 preterm infants, concluded that HFOT has a similar efficacy and safety as the other, more conventional, non-invasive ventilation supports, but causes less nasal trauma (Kotecha et al. 2015).

### 2.2.3.1    Mechanism of action

HFOT washes out nasopharyngeal dead space, thereby reducing overall dead space in the airways and increasing the alveolar ventilation, which constitutes a greater fraction of minute ventilation (Dysart et al. 2009). This dead space reduction is caused by the impact of HFOT on ventilation rates (Dysart et al. 2009) and on the reduction of rebreathing $CO_2$ (Milesi et al. 2014). Further, it is most likely that the work of breathing is reduced due to a reduction of upper airway resistance. Nasopharyngeal flow provided by HFOT should be higher than the patient's own maximal inspiratory flow (Dysart et al. 2009; Haq et al. 2014). In line, there are studies that resulted that higher than a patient's own inspiratory flow provides better oxygen delivery (Milesi et al. 2014). In addition, it is thought that HFOT provides distending pressure, thus assisting gas exchange by remaining alveoli patency (Dysart et al. 2009; Haq et al. 2014).

High flow oxygen therapy must be practised using heated and humidified gas, because cold and dry gas may cause a decrease in pulmonary compliance, mucosal injury, bronchospasm, impaired secretion clearance and patient discomfort (Dysart et al. 2009; Haq et al. 2014). In addition, if heated and humidified gas is used, then the patients do not need to use their own energy to heat and humidity the inhaled gas via nasal mucosa, which reduces the metabolic cost of gas conditioning (Dysart et al. 2009).

### 2.2.3.2    Physiological studies

A prospective observational study compared the flow rate of 2 and 8L/min through nasal cannula of 13 infants under 12 months of age with bronchiolitis. The results of this study showed that the flow rate of 8L/min increased the end-expiratory lung volume and decreased the respiratory rate. Both 2 and 8L/min flows seemed to improve the heart rate and oxygen saturation. (Hough, Pham, Schibler 2014) Another prospective and observational study, which included 25 infants with bronchiolitis, found that nasopharyngeal pressure increased linearly with the flow rate up to 6L/min, and that keeping the mouth open decreased the pressure in comparison to keeping the mouth closed. In addition, bronchiolitis severity scores improved significantly with HFOT. (Arora et al. 2012) A different prospective study with 21 infants under six months of age with bronchiolitis compared the flow rates of 1, 4, 6 and 7L/min. The researchers measured the pharyngeal pressure and found that it increased when the flow increased;

however, only the flows of 6L/min or over provided positive pharyngeal pressure throughout the respiratory cycle. For that reason, the authors concluded that the flow equal to or above 2L/kg/min would generate clinically relevant pharyngeal pressure. (Milesi et al. 2013) Furthermore, another prospective study, which included 28 infants, 14 with bronchiolitis and 14 with congenital heart disease, found that HFOT significantly reduced the work of breathing in bronchiolitis as measured by electrical activity and changes in oesophageal pressure (Pham et al. 2015).

### 2.2.3.3    Descriptive studies

A prospective and observational HFOT study that included 27 infants under 12 months of age with bronchiolitis did not report any adverse events or request for other forms of respiratory support in infant bronchiolitis treated with HFOT. In that study, the median oxygen saturation increased by one to two percentage points and the respiratory rate decreased by 13 to 20 breaths/min after starting the HFOT (Bressan et al. 2013). In another study, the authors, basing their results on three years of experience using HFOT on the ward, reported a decreased heart rate (from 171 to 136, medians) and respiratory rate (from 79 to 53, medians), and improved pH and PCO2 values within four hours of starting HFOT in 45 infants with bronchiolitis. They concluded that HFOT is safe for use on the paediatric ward, because no adverse events were identified and the number of unstable infants decreased. (Kallappa et al. 2014) In a retrospective chart review, all infants who were admitted to the PICU and treated with HFOT were analysed for data after the introduction of HFOT. The intubation rate reduced from 37% to 7% over a five-year period in 167 infants with bronchiolitis. (Schibler et al. 2011) Another retrospective cohort review with 231 infants affected by bronchiolitis found that the intubation rate was 15/231 (6.5%) in infants treated with HFOT. Moreover, risk factors associated with HFOT failure were a triage respiratory rate of more than the 90th percentile for age, an initial venous PCO2 of more than 50 mmHg and an initial venous pH of less than 7.30. (Kelly, Simon, Sturm 2013)

### 2.2.3.4    Comparative studies

A prospective pilot study that included 61 infants under 12 months of age with bronchiolitis compared HFOT to conventional LFOT. In this study, infants who

received HFOT were four times less likely to require a PICU admission. Overall, non-responders could be identified within the first hour - their respiratory and heart rates were stable contrary to the responders whose heart and respiratory rates decreased. The authors also concluded that HFOT is safe to be used on the paediatric ward. (Mayfield et al. 2014)

In another retrospective chart review, which included 113 infants under 12 months of age with bronchiolitis, compared HFOT responders and non-responders. In the 92 who responded to HFOT, the respiratory rate decreased, PCO2 was significantly lower both before and after HFOT, and the Pediatric Risk of Mortality III score was lower, compared to non-responders. (Abboud et al. 2012) Yet another retrospective chart review of 115 infants under 24 months of age with bronchiolitis found that intubation rate decreased from 23% to 9%, and that the median PICU LOS decreased from six to four days after HFOT was introduced (McKiernan et al. 2010). An Italian retrospective chart review found that the LOS in PICU, as well as the oxygenation, did not differ between the infants with bronchiolitis who were treated with nasal continuous positive airway pressure (nCPAP) and those who were treated with HFOT (Metge et al. 2014). In the retrospective pre- and post-intervention study of 290 infants with bronchiolitis, the median LOS in PICU reduced from four to three days after introducing HFOT, but no difference was found in the intubation rate (Riese et al. 2015).

A prospective observational study, including 36 infants under 12 months of age with bronchiolitis, found that the LOS in hospital was three days shorter for those treated with HFOT than for those treated with LFOT. Also, respiratory rate, respiratory effort and ability to eat improved faster in those treated with HFOT. (Milani et al. 2016) Another prospective, randomised open pilot study in 19 infants with bronchiolitis under 12 months of age reported higher median oxygen saturation in those treated with HFOT than in those treated with LFOT. This difference was seen at eight and 12 hours, but no longer by 24 hours. Other measured parameters, such as the total time of oxygen therapy, time to feed orally, time to discharge and the LOS, did not substantially differ between the groups. (Hilliard et al. 2012)

### 2.2.3.5    Summary of high flow oxygen therapy

In summary, the flow rates of 2L/kg/min, or at least over 6L/min, produce sufficient nasopharyngeal pressure and end-expiratory lung volume in infancy.

HFOT seems to reduce breath work, lessen both respiratory and heart rates, and improve oxygen saturation. It has been reported that HFOT is well tolerated and easy to use on the paediatric ward (Bressan et al. 2013; Hilliard et al. 2012; Kelly, Simon, Sturm 2013; Mayfield et al. 2014). However, close monitoring is important because adverse events such as air leaks, abdominal distention, injury of the paranasal sinus and subcutaneous scalp emphysema have been connected to HFOT when non-bronchiolitis patients were treated (Hutchings, Hilliard, Davis 2015).

The lack of well-designed, randomised, controlled studies is obvious. Fortunately, such studies are currently under way. For example, an article on the RCT protocol from Australia and New Zealand has been published recently. In this large, multicentre study, HFOT will be compared to LFOT in 1,400 infants under 12 months of age with bronchiolitis. The primary outcome is treatment failure and secondary outcomes are admission to the PICU, the LOS, the duration of oxygen treatment, the need for other forms of ventilatory support or intubation, and adverse events and costs. (Franklin et al. 2015)


### 2.2.4     Continued positive airway pressure and mechanical ventilation

In a prospective cohort study from the USA, 17% of all 2,207 infants with bronchiolitis were treated in the PICU, and 42% of them were treated with CPAP or mechanical ventilation (MV) - i.e. were intubated. Severe retractions, presence of apnoea, age under two months and oxygen saturation of under 85% in room air were significant predicting factors for CPAP treatment or intubation. Other predicting factors were inadequate oral intake, maternal smoking during pregnancy, low birth weight and the onset of breathing difficulty within one day before admission to the PICU. (Mansbach et al. 2012) In another American study, the intubation rate increased in infants with bronchiolitis between 1997 and 2011: from 5.4% to 13.5% in those with a high risk of RSV, and from 0.7% to 2.4% in those with a low risk of RSV infection (Doucette et al. 2016).

Theoretically, the mechanism of CPAP is positive end-expiratory pressure that increases functional residual capacity and prevents end-expiratory alveolar atelectasis. CPAP might improve both the physiological and clinical outcomes associated with breathing difficulty in bronchiolitis. (Sinha et al. 2015) However, in 2015 the Cochrane review found only two RCTs with 50 infants under 12 months of age. CPAP may reduce MV and respiratory rate, but the effectiveness is still uncertain due to a lack of qualitative evidence. (Jat and Mathew 2015)

Three studies were not included in the 2015 Cochrane review, one prospective population-based study (Oymar and Bardsen 2014), and two retrospective cohort studies (Borckink et al. 2014; Essouri et al. 2014) of infants with bronchiolitis. The prospective study included 46 infants and found that CPAP was well tolerated, with 33 (71.7%) infants treated on the general paediatric ward and only three (6.5%) requiring MV. The LOS in hospital did not differ between those treated on the ward and in the PICU. (Oymar and Bardsen 2014) In the retrospective study of 133 infants with RSV LRTI treated in the PICU, CPAP was associated with shorter ventilatory support (hazard ratio 2.3, 95%CI 1.1-4.7). However, disease severity estimated by the Pediatric Risk of Mortality II Score and by the SpO2/FiO2 ratio was higher in the MV-treated group. (Borckink et al. 2014) Another retrospective study of 525 infants with bronchiolitis demonstrated a decreased length of ventilation (in mean 4.1 vs 6.9 days), shorter LOS in the PICU (in mean 6.2 vs 9.7 days), and less use of MV (12% vs 81%) at the time when CPAP was used as primary ventilatory support in comparison to when the MV was used for primary ventilatory support (Essouri et al. 2014).

The mechanical ventilation is necessary when HFOT or CPAP support is not sufficient. There is no consensus on the best ventilatory technique, nor on the most beneficial adjustments in the vehicles that should be used in the treatment of infants with bronchiolitis. (Oymar, Skjerven, Mikalsen 2014)

## 2.3    Cost of bronchiolitis

The costs of bronchiolitis are high when estimated or evaluated at the national level in different countries. Most studies have evaluated the costs from the viewpoint of the care provider, some studies from the viewpoint of family, but studies from the viewpoint of societies were not found.

In the USA, the total annual charge for bronchiolitis was $1.4 billion, annual total hospitalisation charges were $543 million and the mean hospitalisation charge was $3,799 per hospitalisation from the viewpoint of care providers in 2002 (Pelletier, Mansbach, Camargo 2006). The later estimates of the total annual charge in the USA increased to $1.73 billion in 2009 (Hasegawa et al. 2013a), and the mean hospitalisation charges increased to $25,962 for high-risk infants and $10,289 for other infants in 2012 (Doucette et al. 2016).

In the USA, a quality improvement study evaluated bronchiolitis treatment in the ED before and after the publishing of the AAP' bronchiolitis guidelines. The

average total charge per patient was reduced by $197 (95%CI $136 to $259), and the total charge for the hospitals where the study was done was reduced by $196,406 (Akenroye et al. 2014). The authors estimated as much as $40 million in national savings, if the guidelines were used in every clinic and hospital across the country. These savings were based on reductions in obtaining chest x-rays and RSV tests, and avoidance of salbutamol inhalations. (Akenroye et al. 2014) Another cost-effectiveness study from Canada reported approximately $59 savings per patient when a chest x-ray was not taken routinely, without compromising the diagnostic accuracy of alternative diagnoses (Yong et al. 2009).

In Europe, a prospective randomised controlled study from the UK found £290 savings per patient, if oxygen saturation limit at departure was 90% or over, instead of 94% or over. The total direct hospitalisation charges were £1,612 and £1,902 per patient, respectively. (Cunningham et al. 2015a) In Germany, the average hospitalisation charges were €94 for outpatients with bronchiolitis and €3,551 for inpatients with bronchiolitis (Ehlken et al. 2005). In addition, a prospective multicentre study from Spain reported total ED costs of €249, including €213 direct costs and €36 productive costs. Nationally, the estimation was approximately €20 million for annual costs (Garcia-Marcos et al. 2014). An Italian study reported that preterm infants with bronchiolitis hospitalisation had €7,105 higher average health care charges in their first year of life when compared to the preterm infants without bronchiolitis hospitalisation (Roggeri et al. 2016). Furthermore, another German study reported that the total hospitalisation charge per patient for PICU treatment decreased (€18,801 vs €27,572) if CPAP was used instead of MV for primary ventilatory support (Essouri et al. 2014).

There are only a few studies available on the costs of bronchiolitis from the viewpoint of family. A German study described the major burdens families face when a child develops acute LRTI, such as disturbances to the parent´s sleep, transportation problems and missing the regular family activities. Other burdens were the additional expenses, missed appointments, absence from work and supplemental childcare. (Ehlken et al. 2005) To obtain the total costs of bronchiolitis treatment for families, 14.4% to 15.5% should be added to the costs of bronchiolitis estimated from the viewpoint of health care providers (Garcia-Marcos et al. 2014; Miedema et al. 2001). In the Spanish study, both parents together lost approximately 13.54 work hours while their infant had bronchiolitis, and needed to hire a babysitter for approximately eight hours (Garcia-Marcos et al. 2014).

To summarise the cost of bronchiolitis, the annual costs have increased remarkably in countries where such data are available. The total direct charges varied between the countries depending on the costs accounting of the hospital used and the national price levels. The uses of health care services differ and, furthermore, the costs are higher with bronchiolitis during the first year of life. In addition, bronchiolitis causes an economic burden to families.

## 2.4 Economic evaluation in health care

### 2.4.1 Role of health economics in the allocation of health care resources

Health itself is an important value for both individuals and societies, and a well-functioning health care system can be considered an economic good (Morris, Devlin, Parkin 2009a). The World Health Organization aspires towards universal health care coverage in all countries, meaning that health services can be used by all without suffering financial hardship (Rawlins 2016).

The health care sector is a remarkable part of economies (Morris, Devlin, Parkin 2009a), and the resources used for the health care sector are in correlation to the economic wealth of countries (Rawlins 2016). For example, the relation between health care costs and the gross domestic product for the Organisation for Economic Co-operation and Development (OECD) member countries was approximately 9.0%, and varied between 16.6% (USA) and 5.1% (Turkey) in 2014 (OECD 2016). In Finland, the figure was 9.5% (OECD 2016) and the total costs were €19.4 billion in 2014 (Matveinen and Knape 2016). In the USA, many studies found that health care costs were increasing (Fisher, Bynum, Skinner 2009; Mongan, Ferris, Lee 2008). Broadening the access to health care, as well as the demand for more innovations and better treatments, increases the costs. Still, more cost control is needed. (Mongan, Ferris, Lee 2008) However, the resources for health care are limited in all countries and, therefore, the priorities need to be defined (Rawlins 2016). For that reason, economic evaluation has become an essential part of decision-making in health care policy (Meltzer 2001), covering all levels from planning to management, and health care system evaluations (Chisholm and Evans 2007).

For the purpose of economic evaluations costs may be measured from the viewpoint of the health sector, patient or family, productivity losses or other sectors. The measured effects may include changes in the health stage, resources

saved in the health sector, patient or family, productivity gained, other sector, or other value created (see Figure 3). (Drummond et al. 2015a) The perspective used for evaluations influences the assessment of the benefits and costs of an intervention or a treatment. The perspective of society is the only one that includes all the costs (direct medical, direct non-medical and indirect) which are related to the intervention. Other perspectives that can be used, are the perspectives of the patient, physician, hospital and payer, and those include only some costs. (Meltzer 2001) In addition, decision makers must decide what the acceptance threshold is for a new, more effective, but also more expensive, intervention (Rawlins 2016).

The value of economic evaluations depends on the reliability of the evidence, on the possibility to generalise the results and on the ability to suitably capture the changes in the quality of life (Rawlins 2016). Thus far, economic evaluations have usually been clinical and focused on a particular disease, and, therefore, the efficiency of the health sector as a whole cannot be improved (Chisholm and Evans 2007).

Next comes the introduction of cost analysis and costing methods, the cost-effectiveness analysis, and the decision-analytic modelling, which is also one of the methods to carry out the cost-effectiveness analysis, and these are used in this thesis.

## 2.4.2    Cost analysis

Economic evaluation is understood as an analysis that compares alternative actions (i.e. treatments or interventions), costs and outcomes (Rudmik and Drummond 2013). In general, methods for calculating the costs are common despite the specific economic evaluation methods (Drummond et al. 2015b; Fugel et al. 2016). Costs are dependent on the quantity and combination of the resources used. The costs can be calculated with the following equation:

$$C = \chi_1 x p_{\chi 1} + \chi_2 x p_{\chi 2} + \ldots + \chi_n x p_{\chi n}$$

where C stands for total costs, $\chi$ stands for the quantities of resources used and p is the unit cost of the resource (Morris, Devlin, Parkin 2009b). To simplify this equation, the resources used need to be identified and quantified first, and then they need to be valued (Morris, Devlin, Parkin 2009c). The marked prices are available for many items, but not for all. Those non-marked items need to be valued in another way; one example is to evaluate the items' opportunity cost and to use it. (Drummond et al. 2015b)

The main cost component categories are presented in Figure 3, which is modified from Drummond et al. (2015a). The most important modification is that Drummond et al. (2015a) identified and valuated the resources saved, but in this thesis the value of the resources used is analysed, and so it is added here. The viewpoint of this thesis is marked via the grey colour in Figure 3.

Besides an identification and estimation of the resources, the perspective of evaluation affects the length of the time period that should be chosen. Costs should be tracked, as long as the results of the evaluation do not mislead the decision-maker or user. (Drummond et al. 2015b)

Some criteria lists used for reporting economic evaluations are published. Those can also be understood as the criteria for a qualitative evaluation. The Consensus on Health Economic Criteria (CHEC) list presented five items, which are related to cost directly. The time period and the perspective of the study need to be appropriate, so that relevant costs can be included in the evaluation. In addition, all relevant costs should be identified, measured in physical units and valued appropriately. (Evers et al. 2005) Another Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement presented six items, which are related to cost directly. The perspective is on one item, as well as on the time horizon the other. In addition, the estimating resources and costs, the choice of a discounting rate and cost converting (for example, the year of costs and exchange rate used) are in the statement. The mean values of costs, as well as the mean differences between the groups and, if applicable, the incremental cost-effectiveness ratios should be reported. (Husereau et al. 2013)

The impact of economic evaluations is unfortunately rather low, if measured by adaptation in the practice guidelines. In a December 2015 analysis, under half of the practice guidelines from different medical specialities had adopted at least one economic evaluation. Additionally, only 6% of available economic evaluations were adopted, so it can be concluded that low adoption rate is not only due to a lack of relevant studies. (Zervou et al. 2015)
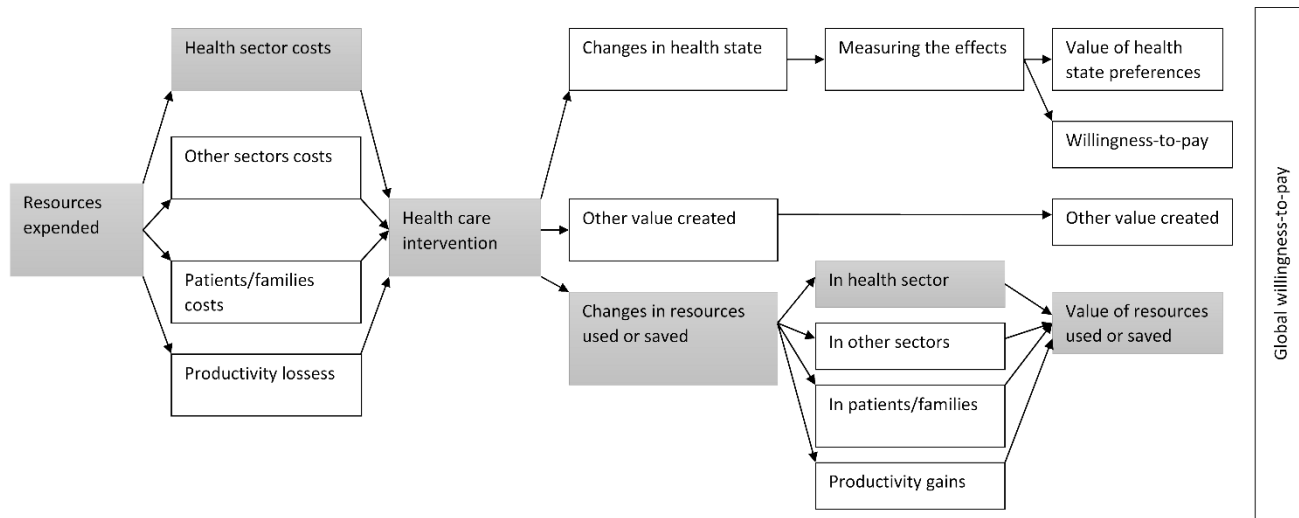
**Figure 3.**   Modified figure of the components of an economic evaluation in health care. First presented is cost, followed by intervention identification possibilities, measuring and valuation (Drummond et al. 2015a).

## 2.4.3 Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) has been regarded as one of the criteria for the implementation of new medical technologies since the late 1980´s (Neumann, Rosen, Weinstein 2005). The CEA is used to evaluate health-related gains in relation to the costs of health interventions (Jamison et al. 2006). Hence, the CEA may help allocate the resources of health care more efficiently (Neumann, Rosen, Weinstein 2005).

The aim of the CEA is to identify how resources can be allocated, such as transferring resources from ineffective to effective interventions, or from less to more cost-effective interventions (Jamison et al. 2006). Nevertheless, the aim of the CEA is to improve the value, not to function as a cost-containment tool, and thus the CEA may, or may not, save money (Neumann, Rosen, Weinstein 2005). This means that the CEA allows losses in potential health benefits to be defined, if the best intervention is not selected for health care use (Neumann and Sanders 2017).

The recommended perspective in the CEA is the societal perspective, but, when a specific decision maker can be identified, other perspectives can be used (Sanders et al. 2016). In the CEA, the costs are usually expressed as direct and productivity costs, and the effectiveness can be measured by a predefined unit of health, such as saved lives, cured disease cases, or better health condition reached (Meltzer 2001). Then, incremental cost-effectiveness ratio (ICER), which is a ratio of the difference in costs between two alternative interventions to the difference in effectiveness between the same interventions, is expressed as a summary of results (Sanders et al. 2016). The other possibility is to present the relationship between costs and effectiveness, which is known as the cost-effectiveness plane (Rawlins 2016). In addition, it is recommended to convey how the results may change with other assumptions, or with other perspectives (Sanders et al. 2016).

Usually, the CEA does not valuate the health outcome and, for that reason, the analyses are hard to compare with each other. That is why the societies´ valuations of the present health conditions affect how the results are applied. (Meltzer 2001) After all, the CEA is just one of many factors that are involved in health care decisions, with some of the other ones being, for example, the patient´s expectations, the ethical and cultural values, as well as legal and political concerns (Neumann and Sanders 2017).

## 2.4.4    Decision-analytic modelling

Decision-analytic modelling is one of the methods to carry out the cost-effectiveness analysis. Both decision-analytic modelling and CEA provide a systematic approach to quantitatively integrate the evidence of specific intervention (Ryder et al. 2009). Therefore, various interventions can be quantified and compared in decision-analytic modelling (Ademi et al. 2013). Decision-analytic modelling is a mathematical modelling method. It uses the existing evidence to create its model, and evaluates the consequences of the decisions made by that model. (Werner, Wheeler, Burd 2012) Modelling analyses are usually used when direct research is not possible, when we need to predict or to understand the real or hypothetical practices, and when decision making needs assistance (Stahl 2008). Decision-analytic modelling is especially useful for situations that are associated with high uncertainty (Ademi et al. 2013).

The aim of decision-analytic modelling is to identify actions, such as treatment methods, that will have the most health gain in complex and uncertain situations (Ryder et al. 2009).

Decision-analytic modelling consists of multiple components (Werner, Wheeler, Burd 2012), and the most important one is clinical decision. The analyses are carried out by first identifying the decision problem and all decision alternatives, then by listing all possible outcomes, defining time-related horizons and designing the sequence of events that lead from the original decision to the outcomes and to secondary decisions. Lastly, the uncertainty is quantified in decision-analytic modelling, values are also quantified and the expected values for each decision are calculated. (Ryder et al. 2009) In sensitivity analyses, there is a possibility to vary the probabilities and values input into decision-analytic modelling and, thus, to see how these changes affect the results of the decision-analytic modelling (Ryder et al. 2009). Consequently, sensitivity analyses are used to examine the probabilities of the event or outcome of a modelled strategy, and to examine the uncertainty surrounding the decisions (Stahl 2008).

In this thesis, the decision-analytic modelling are carried out using decision trees, which is one possible method by which analysis can be performed (Ryder et al. 2009), as well as Markov models (Stahl 2008). Decision trees consist of a decision node (usually presented by a square), branches, change nodes (usually presented by a circle) and outcome nodes (usually presented by a triangle) (Ryder et al. 2009; Stahl 2008). In a decision tree model it is possible to compare two or

more options, and many secondary decisions can be examined (Ademi et al. 2013).

Decision-analytic modelling also has its limitations, as do all other analysis methods. The value of the results depends on the quality of data used to identify the decisions and to estimate the probabilities and outcomes (Werner, Wheeler, Burd 2012). Additionally, decision analysis may be impractical in a clinical context, and may over-simplify complex medical problems and health values (Ryder et al. 2009).

### 2.4.5 Summary of the economic evaluation in health care

Health care expenditures have risen because more services are used and the prices of those services have increased (Klein, Brown, Detsky 2016). The economic evaluation in health care is essential for the allocation of resources, so that it is possible to achieve better health outcomes (Jamison et al. 2006). Many different economic analyses have thus far been introduced, such as the CEA.

In this thesis, cost analysis and CEA by decision tree are used that are based on the viewpoint of the health care provider. One of the targets is to evaluate whether the studied treatments for infant bronchiolitis are more effective and, hopefully, less expensive or, if not less expensive, at least possess an acceptable cost-effectiveness ratio. The purpose of this thesis is to identify the costs of bronchiolitis hospitalisation and to find some possibilities to save resources.

# 3  AIMS OF THE STUDY

The primary aims of this thesis were to evaluate the hospitalisation costs of bronchiolitis, the cost-effectiveness of high flow oxygen therapy (HFOT) in comparison to low flow oxygen therapy (LFOT), and the cost-effectiveness and effectiveness of hypertonic saline (HS) inhalations in comparison to normal saline (NS) inhalations or to standard treatment in infant bronchiolitis. The target was to provide information to assist the decision making with respect to alternative treatments in hospitalised infants. In this thesis, the viewpoint of health care providers was used.

The more specific aims were:
- To evaluate the hospitalisation costs of bronchiolitis in the emergency department, on the paediatric ward and in the paediatric intensive care unit, as well as the factors that were associated with higher costs. Additionally, annual variations and possible trends in costs from 2000 to 2012 were evaluated (I).
- To evaluate the cost-effectiveness of HFOT in comparison to standard LFOT in bronchiolitis treatment (II).
- To evaluate the cost-effectiveness of HS inhalations in comparison to NS inhalations or to standard treatment without inhalations in infant bronchiolitis (III).
- To evaluate the effectiveness of HS inhalations in comparison to NS inhalations or standard treatment without inhalations in infant bronchiolitis in relation to time from 2003 to 2017, by using cumulative meta-analysis (IV).

# 4  MATERIALS AND METHODS

## 4.1  Study design

This thesis was based on the retrospective case-control research frame. We identified infants under 12 months of age with the diagnosis of bronchiolitis from the Tampere University Hospital electronic registers.  As cases, we selected all infants who were treated for bronchiolitis at under 12 months of age in the paediatric intensive care unit (PICU) from 2000 until 2012 (a total of 80 cases). For each case, we selected two controls that were treated for bronchiolitis in the emergency department (ED), one just before and the other just after the case. These controls were either treated only in the ED or also on the paediatric ward, but not in the PICU. The costs of the bronchiolitis treatment in the hospital was evaluated from the viewpoint of the care provider.

The patient and cost data were used for modelling the cost-effectiveness analyses of high flow oxygen therapy (HFOT) and hypertonic saline (HS) inhalation therapy in infant bronchiolitis. For the purposes of this modelling, we performed a literature search through PubMed to find the data available on the effectiveness of the HFOT in comparison to low flow oxygen therapy (LFOT), as well as another literature search to find the data available on the effectiveness of the HS inhalations in comparison to normal saline (NS) inhalations. Subsequently, we performed a third literature search via PubMed and Scopus to evaluate, in more detail, the effectiveness of the HS inhalations in comparison to NS inhalations or treatment with no inhalations, by using cumulative meta-analysis. The description of the used methods, main outcome, population and data sources applied in each sub studies is presented in Table 1.

**Table 1.**   Description of the methods and data sources applied in each sub studies

| Sub study | Methodological content |
|---|---|
| **I: Cost analysis** | *methods:* case-control study<br>*main outcome:* hospitalisation costs<br>*population:* infants <12 months with bronchiolitis treated in the PICU (cases) or on the ward or in the ED (cases)<br>*data sources:* electronic data and patient registers from theTampere University Hospitals |
| **II: Cost-effectiveness analysis:** | *methods:* decision tree analysis<br>*main outcome:* cost-effectiveness of HFOT compared to LFOT<br>*population:* infants with bronchiolitis<br>*data sources:* cost data from the cost analysis (I) and data on the effectiveness from earlier published studies (searched from PubMed) |
| **III: Cost-effectiveness analysis:** | *methods:* decision tree analysis<br>*main outcome:* cost-effectiveness of HS compared to control treatment<br>*population:* infants with bronchiolitis<br>*data sources:* cost data from the cost analysis (I) and data on the effectiveness from earlier published studies (searched from PubMed) |
| **IV: Effectiveness analysis:** | *methods:* cumulative meta-analysis<br>*main outcome:* effectiveness of HS compared to control treatment<br>*population:* infants with bronchiolitis<br>*data sources:* data on the effectiveness from earlier published studies (searched from PubMed and Scopus) |

## 4.2    Data collection

### 4.2.1    Patient data (I)

We identified 80 infants admitted for bronchiolitis at the age of less than 12 months between the years 2000 and 2012, which constitute the cases for the

present study. As controls for these cases we selected 160 infants who were treated in the ED (n=56) or on the ward (n=104), but were not treated in the PICU. The data of these 80 cases and 160 controls were used to study the costs of bronchiolitis treatment.

We used a structured form when we collected the basic and medical data from electronic or paper patient registers. We recorded the dates of admission and departure, number of gestation weeks, age on admission, gender, presence of bronchopulmonary dysplasia (BPD), and presence of doctor-diagnosed allergy and doctor-diagnosed asthma in parents or siblings. We also made a record whether oxygen support, HFOT, nasal continuous positive airway pressure (nCPAP) or mechanical ventilation were used, and whether the administration of fluids via the nasogastric tubes or intravenous route was needed, as well as whether inhaled racemic adrenaline, inhaled beta-agonists or inhaled 0.9% or 3% saline was used.

### 4.2.2    Cost data (I)

We collected the cost data from the electronic files of the Tampere University Hospital. For the years 2000 to 2012, we collected the costs of daily municipal billing for every case and control patient included in our study. The billing was based on either expense categories and/or on the Nordic Diagnosis Related Groups (NordDRG) system. Only expense categories were used from 2000 to 2006, and both expense and NordDRG categories from 2007 to 2012.

The doctor responsible for the infants' treatment defined the expense category or the NordDRG category on a daily basis. Both categories were constructed to cover all hospital expenses such as nursing, medication and other treatments, diagnostic tests, staff salaries and even property overheads. To summarise, the costs represented the actual municipal billing sums for every patient. We did not estimate the costs, nor did we use average sums of costs.

We transformed the costs between 2000 and 2012 to the 2012 level by using the Association of Finnish Local and Regional Authorities' hospital financing index. Thereafter, we calculated the total costs of the hospitalisation and the costs per treatment day separately for the ED, the ward and the PICU expenditures.

### 4.2.3　Incremental cost-effectiveness ratio and cost-effectiveness plane

When modelling the cost-effectiveness analyses we estimated the incremental cost-effective ratios (ICER) for the treatments. ICER describes the change in costs when one additional unit of effectiveness is gained. We calculated ICER, when possible, using the equation:

$$\text{ICER} = (C_{\text{Intervention}}-C_{\text{Control}})/(E_{\text{Intervention}}-E_{\text{Control}})$$

where C stands for the cost and E for the effectiveness.

However, if the C/E ratios were to include negative numbers, then methods other than ICER are needed to analyse the cost-effectiveness, because the negative ICER value is not unambiguous anymore (Stinnett and Mullahy 1997). The cost-effectiveness plane is a fourfold table, where a new intervention is compared to a control treatment (Briggs and Fenn 1998). The control treatment is placed at the origin, and the intervention is placed dependant on the costs and effectiveness of the intervention when compared to the control. In the cost-effectiveness plane, the x-axis illustrates the effectiveness (the intervention is less effective than the control when it is on the left side of the axis, while on the right it is more effective) and the y-axis illustrates the costs (the intervention is less expensive than the control when on the down side of the axis, while on the upper side it is more expensive) (Figure 4).
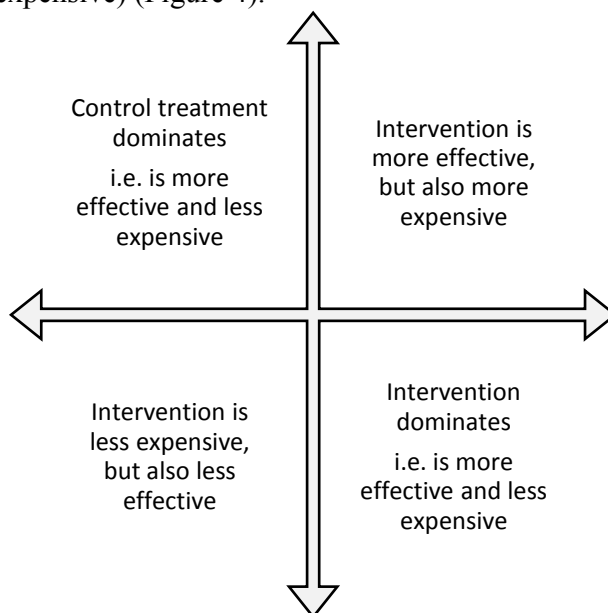


**Figure 4.**　The cost-effectiveness plane: comparing the intervention to the control (modified from Briggs and Fenn 1998).

### 4.2.4    Literature search (II, III, IV)

To examine the effectiveness of HFOT we performed a literature search through
PubMed up to January 2015. We used "bronchiolitis", "high and/or flow and/or
nasal and/or cannula", and "ventilatory and/or support" as the search terms. Our
search identified 96 studies in total, from which we then selected 38/96 based on
the title heading, narrowing them down further on the basis of the abstract to
12/38  and then upon the examination of the full paper to 4/12 (Kelly, Simon,
Sturm 2013; Mayfield et al. 2014; McKiernan et al. 2010; Schibler et al. 2011).

   Two of those studies were done in the USA and two in Australia. Three of the
studies were retrospective chart reviews that compared the periods before and
after the introduction of HFOT, and one was a prospective pilot study whose aims
were to gather clinical data on the safety and clinical impact of HFOT use in a
ward situation (Table 2).

**Table 2.** Previous studies on the effects of high flow nasal cannula treatment (original article II).

| Basic study details | The study protocol | Main results |
|---|---|---|
| Mayfield et al. 2014<br><br>Australia | Prospective controlled pilot study, including 61 cases treated with HFNC admitted to the ward and 33 retrospectively selected controls treated on the ward at the same time as the cases. Infants hospitalised for bronchiolitis at less than 12-months-of-age.<br><br>Comparison of the treatment effects between HFNC and standard treatment groups. | In the HFNC group, eight (13%) patients were admitted to the PICU, compared to 10 (31%) in the standard treatment group.<br><br>LOS and length of treatment did not differ between the groups. |
| Kelly et al. 2013<br><br>USA | Retrospective chart review of 231 infants hospitalised for bronchiolitis at less than 24-months-of-age.<br><br>Evaluation of patient characteristics that predict success or failure of HFNC. | In infants treated with HFNC, the intubation rate was 15/ 231 (6.5%). |
| Schibler et al. 2011<br><br>Australia | Retrospective chart review of 167 infants hospitalised in the PICU for bronchiolitis at less than 24-months-of-age.<br><br>Comparison of the treatment effectiveness before and after using HFNC. | HFNC reduced the need for intubation from 37% to 7%. However, 25% of infants needed other non-invasive ventilation support.<br><br>Median LOS was 1.83 d (HFNC), 3.75 (HFNC+NIV), 9.35 (HFNC+NIV+IV) and 16.9 (HFNC+IV). |
| McKiernan et al 2010<br><br>USA | Retrospective chart review of 115 infants hospitalised in the PICU for bronchiolitis at less than 24-months-of-age.<br><br>Comparison of the treatment effectiveness before and after using HFNC. | HFNC reduced the need for intubation from 23% to 9%.<br><br>PICU stay was reduced from six days to four days (p=0.0058). |

LOS, length of hospital stay; HFNC, high flow nasal cannula; NIV, non-invasive ventilation; IV, invasive ventilation. The term high flow nasal cannula (HFNC) treatment was replaced in this thesis by the term high flow oxygen therapy (HFOT).

For the study of the effectiveness of the HS inhalations, we performed a first literature search via PubMed between May 2013 and April 2016, and the second search via PubMed and Scopus up to the 20th of June 2017. We used the search terms "bronchiolitis" and "hypertonic and/or saline" for both.

The first literature search was designed to identify all randomised controlled trials (RCT) that compared ≥3% HS inhalations to NS inhalations or no inhalation treatment in infant bronchiolitis, which were published after the data collection in the 2013 Cochrane review. The earlier studies were chosen from the Cochrane review. During this literature search we defined bronchiolitis as the first breathing difficulty induced by an acute viral lower respiratory tract infection (LRTI) at under 24 months of age.

Our search identified 111 studies in total, from which we selected 29/111 on the basis of the title, narrowing this down to 16/29 after reading the abstract and to 10/29 studies after reading the full paper. Thus, the data collected on the effectiveness of HS inhalations in infant bronchiolitis consisted of the 2013 Cochrane review and of ten RCTs published after the review.

In the second literature search, we identified 133 studies from PubMed and 183 studies from Scopus. In addition, we used the "snowball method" and searched for more literature within the recently published reviews and meta-analyses (Brooks, Harrison, Ralston 2016; Maguire et al. 2015; Overmann and Florin 2016; Zhang et al. 2015), and identified 82 studies. We did the PICOS (population, income, comparison, outcome, study) analysis to define the inclusion criteria (Table 3).

**Table 3.** PICOS criteria for the cumulative meta-analysis of HS inhalations in infant bronchiolitis (modified from the original article IV).

| | |
|---|---|
| Population | Infants with bronchiolitis. Bronchiolitis was defined as the first breathing difficulty induced by an acute LRTI at under 24 months of age. |
| Intervention | Hypertonic (≥3%) saline inhalations with or without adrenaline, bronchodilator or other adjunct treatment. |
| Comparison | Isotonic (0.9%) saline inhalations with or without adrenaline, bronchodilator or other adjunct treatment, or no comparable intervention (i.e. standard treatment without any inhalations). |
| Outcome | Length of the hospital stay, if the patients were treated as inpatients (mean and standard deviation), and the hospital admission rate, if the patients were treated as outpatients (events / number of infants). |
| Study | Published RCT. |

From accepted studies, we collected the name of the first author, the country and the publication year. In addition, the number of infants in the all study groups, the upper age limits used and the average age of infants on admission were collected, as well as the intervention used (HS concentration) and the doses given, the comparator used and the doses given, adjunctive therapy if used, the hospital stay (mean and standard deviation, SD) and the admission rate as a number of events, as well as the numbers of all infants in the study groups.

## 4.3    Statistical analyses (I)

We performed an exploratory analysis and found that the costs were non-normally distributed. Nevertheless, we expressed the results as proportions, means and 95% confidence intervals (95%CI) and ranges. This decision was made because the mean cost better illustrates the costs at the population level, tough the median cost better illustrates the costs at the individual level.

Costs per patients were analysed using Spearman´s correlation and the analysis of variance. We used the Mann-Whitney U–test for continuous variables and the chi-square test for categorised variables.

Linear regression analysis with logarithmic transformation was used for cost per patient per day in univariate and multivariate analyses for the PICU group. For multivariate analysis, the treatment year, age on admission, gestational age, gender, allergy, family asthma and LOS in the PICU were used as covariates.

We performed the analyses with SPSS 21 software (SPSS Inc., Chicago, IL, USA).

## 4.4 Decision-analytic modelling (II, III)

We used decision-analytic modelling, the decision tree to be precise, when evaluating the cost-effectiveness of HFOT in comparison to standard LFOT, as well as the cost-effectiveness of HS in comparison to controls in bronchiolitis treatment. We used two different models in the analyses. We performed the analyses with TreeAge Pro version 2015 (TreeAge Software, Inc., Williamstown, USA).

### 4.4.1 Models in the high flow oxygen therapy study

Model One was constructed using the mean total cost of the hospitalisation, the probabilities of PICU treatment and the effectiveness of the treatment (Figure 5). Model Two was constructed using the mean cost per day multiplied by the LOS in the hospital, the probability of PICU admission, the different ventilatory supports that were needed and the effectiveness of the treatment (Figure 6). Inpatient costs were included in the analysis only, and the endpoint at all branches was the discharge of the patient in both models.

c, costs as Euros; e, effectiveness; p, probability; HFNC, high flow nasal cannula (that is, high flow oxygen therapy, HFOT); TT, standard treatment (that is, low flow oxygen treatment, LFOT).

**Figure 5.** The decision tree for Model One: HFOT in comparison to LFOT in infant bronchiolitis (original article II).



c, costs as Euros; e, effectiveness; p, probability; HFNC, high flow nasal cannula (that is, high flow oxygen therapy, HFOT); ST, standard treatment (that is, low flow oxygen treatment, LFOT); NIV, non-invasive ventilation; IV, invasive ventilation.

**Figure 6.** The decision tree for Model Two: HFOT in comparison to LFOT in infant bronchiolitis (original article II).

### 4.4.2 Probabilities in the high flow oxygen therapy study

In both models, we presumed that 6% (Jartti et al. 2014; Pruikkonen et al. 2014) of infants hospitalised for bronchiolitis were treated in the PICU if standard LFOT was used. We presumed that the PICU admission rate would be reduced if HFOT was used, as HFOT would reduce the intubation rate.

HFOT can be used on the ward, but infants who need other ventilatory support are treated in the PICU. For this reason, we supposed that the need for other ventilatory support, as well as the need for PICU treatment, would be reduced.

The probability (P) of PICU admission in infants with bronchiolitis hospitalisation was calculated using the following equation:

$$P = y - \frac{y \times \int b - y \times \int a}{100}$$

where P stands for the probability of PICU admission (%), y for the PICU admission rate before HFOT, $\int b$ for the intubation rate when HFOT was not in use and $\int a$ for the intubation rate when HFOT was in use.

In the second model, there were four different ventilatory support arms in the PICU treatment: non-invasive ventilation only, invasive ventilation only, both invasive and non-invasive ventilation, and a different reason for PICU treatment. We obtained the probabilities for those arms from infants with bronchiolitis who were treated with HFOT in the Australian study (Schibler et al. 2011), and from our own data of 74 infants with bronchiolitis treated in the PICU without HFOT.

### 4.4.3 Effectiveness of the treatment in the high flow oxygen therapy study

In the previous studies on HFOT, the intubation rate was reduced from 23% to 9% in 115 infants (McKiernan et al. 2010) and from 37 % to 7% in 167 infants (Schibler et al. 2011) when HFOT was used in the PICU. Additionally, the use of HFOT reduced the need for intensive care from 31% to 13% in 93 infants treated on the ward. HFOT did not shorten the LOS in the only prospective study (Mayfield et al. 2014).

When HFOT was used, we measured the effectiveness (E) as the reduction of the PICU admission rates in relation to the reduction of the intubation rate in bronchiolitis and used the following equation:

$$E = 1 + \frac{y - P}{100}$$

where E stands for the effectiveness of HFOT, P for the probability of PICU admission (%) if HFOT was used, and y for the PICU admission rate without HFOT. The comparable effectiveness was set at one.

### 4.4.4 Sensitivity analyses in the high flow oxygen therapy study

We did several sensitivity analyses for models one and two, because the probabilities and the effectiveness of HFOT was still quite uncertain. We varied the PICU admission rate (from 4.2% to 13% for HFOT, and from 6% to 31% for LFOT), the probabilities of different ventilatory support and the effectiveness of HFOT (from 1.0 to 1.2). In addition, we varied the costs (median costs, the lower and upper limits of the 95%CI) and the LOS (median LOS, the lower and upper limits of the 95%CI).

Besides sensitivity analyses, we also carried out three worst-case scenario analyses for Model Two. In scenario one, we applied the upper limits of the 95%CI for both the LOS and the costs in the HFOT branch, and the respective lower limits in the LFOT branch. In worst-case scenarios two and three we applied mean costs to both branches, but used the upper limit of 95%CI to the LOS for the HFOT branch, and a lower limit of 95%CI to the LOS for the LFOT branch. The limits for the LOS for worst-case scenario two were obtained from the study by Schibler et al. (2011), and for worst-case scenario three from our own 2000 to 2012 data.

### 4.4.5 Models in the hypertonic saline study

We analysed the hospitalisation rate in the outpatient setting in Model One, and the LOS in hospital in the inpatient setting in Model Two. All decision trees were run three times: first with the details of the meta-analysis from the studies included in the 2013 Cochrane review, second with the details of the meta-analysis with later studies not included in the 2013 Cochrane review, and third with the details of the meta-analysis of all these studies together. We selected this strategy since the results of the studies were conflicting, especially between those included in the Cochrane review and those published after it.

Model One was constructed using the mean costs per admission, the probability of hospitalisation and of PICU admission after hospitalisation and the effectiveness of treatment (Figure 7). Model Two was constructed using the mean

costs per day multiplied by the LOS, the probability of PICU admission, and the effectiveness of the treatment (Figure 8). Both inpatient and outpatient costs were included in Model One, but only inpatient costs were included in Model Two. In both models, we used the same hospitalisation costs for both branches, because the price of HS (max. €0.18/dose) and NS (max. €0.16/dose) solutions were similar, and the small difference in price did not substantially affect costs. The endpoint of the branches was the discharge of the patient in both models.
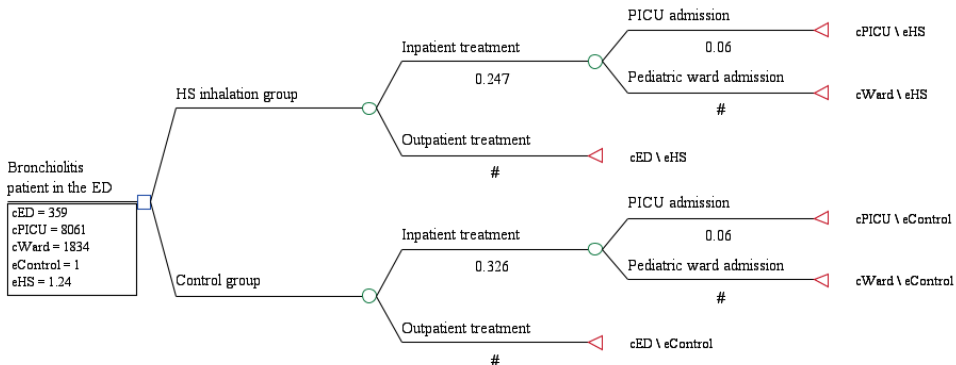


c, cost; e, effectiveness; ED, emergency department; PICU, paediatric intensive care unit.

**Figure 7.** The decision tree for Model One: HS inhalations in comparison to controls in infant bronchiolitis in the ED (original article III).
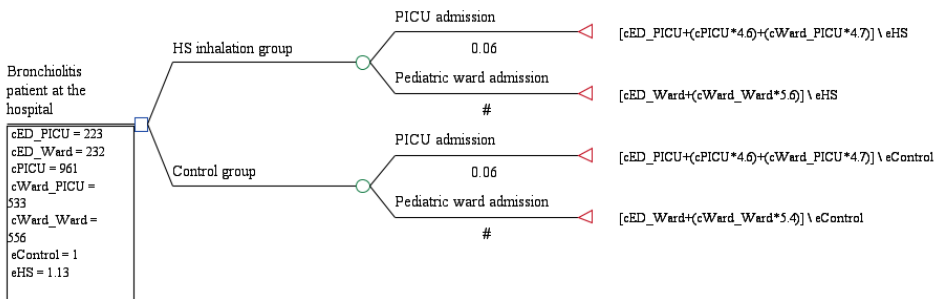


c, cost; e, effectiveness; ED, emergency department; PICU, paediatric intensive care unit.

**Figure 8.** The decision tree for Model Two, HS in comparison to control in infant bronchiolitis in the hospital (original article III).

### 4.4.6 Probabilities in the hypertonic saline study

For Model One, the probability of being treated as an inpatient was considered to be the hospitalisation rate calculated from the meta-analyses. In both Model One and Model Two, we presumed that 6% (Jartti et al. 2014; Pruikkonen et al. 2014) of infants hospitalised for bronchiolitis were treated in the PICU.

### 4.4.7 Effectiveness of the treatment in the hypertonic saline study

We evaluated the effectiveness of HS inhalations from the meta-analyses completed separately in the studies included in the 2013 Cochrane review, the later studies not included in this review and all studies. The measure of effectiveness was the change in the hospitalisation rate and in the LOS in hospital in the HS inhalation group, in relation to the hospitalisation rate or the LOS in hospital of the control group. This was calculated using the equation:

$$E = 1 + \frac{\int control - \int hs}{\int control},$$

where E stands for effectiveness, $\int$ control for the admission rate (%) or LOS in days in the control group, and $\int$ hs for the admission rate (%) or LOS in days in the HS inhalation group.

In the control group, the effectiveness was set to 1.0. The effectiveness was only calculated when the difference in the hospitalisation rate, or in the LOS in hospital, between the HS inhalation and control groups was statistically significant in the meta-analysis. If there was no statistically significant difference, the effectiveness was set to 1.0 for both groups.

### 4.4.8 Sensitivity analyses in the hypertonic saline study

Because of conflicting results in the available studies, we performed numerous sensitivity analyses. We performed the decision tree analyses with the results of every single study separately. In addition, we carried out the decision tree analyses with varying costs (the upper and lower limits of the 95%CI), and varying hospitalisation rates and the LOS in hospital.

## 4.5    Meta-analysis (III, IV)

HS inhalations in bronchiolitis treatment have been widely studied since the year 2003. Previously published results of the effectiveness of HS inhalations were confounding. We used meta-analysis to analyse the effectiveness of the HS inhalations in comparison to NS inhalations, or to standard treatment without inhalations.

Meta-analysis is a quantitative, statistical procedure used to integrate the results of several single studies, and to produce estimates to summarise the overall results. The meta-analysis provides a strong research frame, because the number of participants is large, which increases the statistical power and, consequently, decreases the risk of type-2 statistical error (Crowther, Lim, Crowther 2010; Haidich 2010; Nordmann, Kasenda, Briel 2012). Important problems to be considered in the interpretation of the results of meta-analyses are the heterogeneity between or within the original studies, as well as the publishing and selection biases (Higgins et al. 2003; Sterne et al. 2011). By cumulative meta-analysis, the beneficial and harmful effects of treatments can be found as early as possible. With cumulative meta-analysis, the temporal or chronological chances are seen (Clarke, Brice, Chalmers 2014; Pogue and Yusuf 1997).

We used the random effect model in all meta-analyses, because it is suitable in cases when the researcher cannot be sure that all data is included in the meta-analysis, and when the effect size varies between studies, which is something we came across.

The effectiveness of the HS inhalations given on the paediatric ward, in comparison to the controls, is presented using the mean difference (MD) in the LOS and its 95%CI. The effectiveness of the HS inhalations given in the ED, in comparison to the NS inhalations, is presented using the risk ratio (RR) for the hospital admission rate and its 95%CI. Standard meta-analysis was used in the original article III and cumulative meta-analysis in the original article IV.

We evaluated the heterogeneity between the studies using the Higgins $I^2$ test in both standard and cumulative meta-analysis. The $I^2$ value (as %) describes the variation across the studies that is due to heterogeneity, but not randomly due to chance (Higgins et al. 2003). We used the Cochrane Handbook recommendation for interpreting the $I^2$ value as follows: 0% to 40% no important heterogeneity, 30% to 60% moderate heterogeneity, 50% to 90% substantial heterogeneity and 75% to 100% considerable heterogeneity (Higgins and Green 2011).

We used the funnel plot graphics and Egger´s test when analysing the publication bias in both the overall analyses and the subgroup meta-analyses. A funnel plot is a scatter plot where all the estimated effects from original studies are placed against the standard error of the effect estimates. The effect estimates are usually placed on the horizontal axis and the standard error of the effect estimates on the vertical axis, so that the larger, most powerful studies are placed towards the top. (Sedgwick 2013; Sterne et al. 2011) The plot will resemble a symmetrical inverted funnel if there is neither a between-study heterogeneity nor a reporting bias (Sterne et al. 2011); thus, an asymmetrical plot reflects a reporting bias (Sedgwick 2013). The Egger´s test is a statistical test to indicate the funnel plot symmetry, and the null hypothesis is that such symmetry exists (Sedgwick 2013).

The Cochrane Handbook recommends analysing and reporting the funnel plots only if the meta-analysis includes ten or more studies, because with fewer studies the method does not have enough power to reveal real asymmetry. In addition, funnel plots are suitable for continuous outcomes, as well as the Egger´s test, but in the case of dichotomous outcomes, funnel plots are suitable only for obtaining an odds ratio. Thus, the risk ratio has been less studied and firm guidance is not yet available. (Higgins and Green 2011) For this reason, we did not use Egger´s test when analysing the hospital admission rates (IV).

We performed the meta-analyses using the Review Manager (RevMan Computer program, version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014) and the Comprehensive Meta-Analysis software (version 3.3.070, 2014, Biostat Inc., Englewood, NJ, USA).

# 5   RESULTS

## 5.1     Description of the patient data (I)

Infants treated in the PICU because of bronchiolitis were more often prematurely born when compared to those treated on the ward or in the ED (Table 4). They were also younger at the time of admission (Table 4).

**Table 4.**    Basic characteristics of the infants treated in the PICU (cases) and in the ED or on the ward (controls) for bronchiolitis from 2000 to 2015 (modified from the original article I).

|  | Cases n=80 in 2000-2012 | Controls n=160 in 2000-2012 |
|---|---|---|
| **Gender (boys) % (n)** | 58.8 (47) | 58.1 (93) |
| **Age (weeks) mean (95%CI)** | 13 (10-15) | 21 (19-24) |
| **Gestational age (weeks) mean (95%CI)*** | 34.6 (33.3-35.8) | 38.7 (38.3-39.1) |
| **BPD % (n)** | 8.8 (7) | 0.6 (1) |
| **Allergy % (n) ^** | 3.9 (3) | 6.3 (10) |
| **Family asthma % (n)** | 10 (8) | 15.6 (20) |

BPD, bronchopulmonary dysplasia; 95%CI, 95% Confidence Interval. Allergy is defined as doctor diagnosed atopic dermatitis or food allergy in infants. Family asthma is defined as doctor diagnosed asthma in parents or siblings. * Data is missing in three cases and seven controls, ^ data is missing in three cases.

The average LOS in hospital was 10 days (95%CI 8.1-11.2) for infants treated in the PICU compared to three days (95%CI 2.7-3.5) for those treated on the ward.

## 5.2    Hospitalisation costs between the years 2000 and 2012 (I)

The mean total hospitalisation costs were €8,061 (95%CI €6,193-9,929) if the infants were treated in the PICU, and €1,834 (95%CI €1,649-2,020) if the infants were treated on the ward (Table 5). The mean costs on the ward were much higher if the infants were also treated in the PICU. However, the costs per treatment day on the ward and ED costs were equal.

**Table 5.**    The hospitalisation costs per patient and per treatment day for each patient in Euros. Hospitalisation costs were presented separately for those infants treated in the PICU, on the ward and in the ED (modified from the original article I).

|  |  | **PICU patients (n=80) mean (95 % CI)** | **Inpatients (n=104) mean (95 % CI)** | **Outpatients (n=56) mean (95 % CI)** |
|---|---|---|---|---|
| **Costs € / patient** | ED | 236 (216 – 255) | 248 (231 – 264) | 359 (331 – 387) |
|  | Ward | 3,577 (2,437 – 4,718) | 1,587 (1,402 – 1,771) |  |
|  | PICU | 4,877 (3,560 – 6,194) |  |  |
|  | Total | 8,061 (6,193 – 9,929) | 1,834 (1,649 – 2,020) | 359 (331 – 387) |
| **Costs € / treatment day** | ED | 223 (212 – 237) | 232 (222 – 243) | 359 (331 – 387) |
|  | Ward | 533 (478 – 565) | 556 (524 – 588) |  |
|  | PICU | 961 (739 – 983) |  |  |
|  | Total | 768 (625 – 770) | 677 (636 – 719) | 359 (331 – 387) |

ED, emergency department; PICU, paediatric intensive care unit.

In the PICU treated-cases, the hospitalisation costs were higher if the infants were born preterm. The mean total hospitalisation costs were €6,337 (95%CI €3,929-8,745) (<37 weeks of gestation), €10,108 (95%CI €6,980-13,237) (between 32 and 37 weeks of gestation) and €10,575 (95%CI €7,556-13,595) (>37 weeks of gestation), respectively.

The total hospitalisation costs correlated strongly with the LOS in hospital (r=0.960; p<0.001) and with the LOS in the PICU (r=0.681; p<0.001). A weaker, though significant, correlation was seen with gestational age (r=-0.346; p<0.001) and with age upon hospital admission (r=-0.344; p<0.001). In the multivariate linear regression analysis, the LOS in the PICU and the treatment year were, however, the only factors that retained statistical significance (original article I).

## 5.3 Cost-effectiveness of the high flow oxygen therapy (II)

The probabilities (P) for the PICU treatment were 0.0516, 0.042 and 0.13, and the effectiveness (E) values were 1.0084, 1.018 and 1.18, respectively, when HFOT was used. For LFOT, we settled P to 0.06 and E to 1.0.

The expected hospitalisation costs per patient in Model One were €2,153 for HFOT in comparison to €2,208 for LFOT when P was 0.0516 and E was 1.0084 (Figure 9). The expected costs varied from €1,748 to €2,428 for HFOT, and from €1,777 to €2,495 for LFOT depending on which cost level was included in the model (median, lower or upper limit of 95% CI).
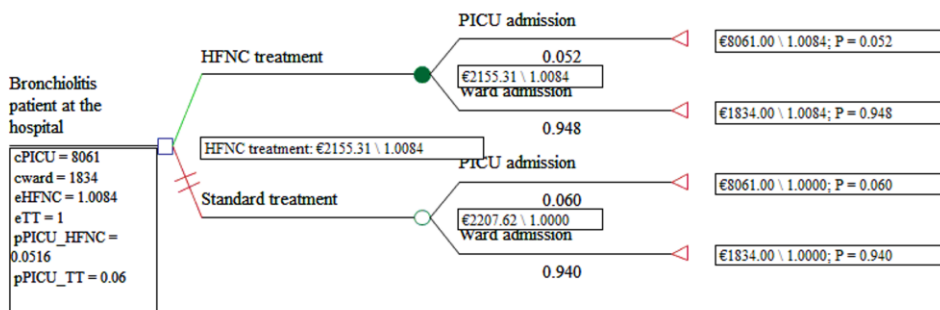


c, costs in Euros; e, effectiveness; p, probability; HFNC, high flow nasal cannula (that is, high flow oxygen therapy, HFOT); TT, standard treatment (that is, low flow oxygen treatment, LFOT).

**Figure 9.** The outcome for Model One (original article II).

With the other P and E values, the expected costs varied between €2,096 and €2,644 for HFOT, and between €2,208 and €3,764 for LFOT.

The ΔC was €-55 and varied between -29 and -67, and the ΔE was 0.0084 when P was 0.0516. Because of the negative value, the ICER is not presented.

HFOT remained more cost-effective in comparison to LFOT in all sensitivity analyses in Model One.

The expected hospitalisation costs per patient in Model Two were €1,326 for HFOT in comparison to €1,598 for LFOT when P was 0.0516 and E was 1.0084 (Figure 10). The expected costs varied from €1,230 to €1,396 for HFOT, and from 1,465 to €1,680 for LFOT depending on which cost level was included in the model (median, lower or upper limit of 95% CI). With the other P and E values, the expected costs varied between €1,312 and €1,442 for HFOT, and between €1,598 and €2,654 for LFOT.



c, costs in Euros; e, effectiveness; p, probability; HFNC, high flow nasal cannula (that is, high flow oxygen therapy, HFOT); ST, standard treatment (that is, low flow oxygen treatment, LFOT); NIV, non-invasive ventilation; IV, invasive ventilation.
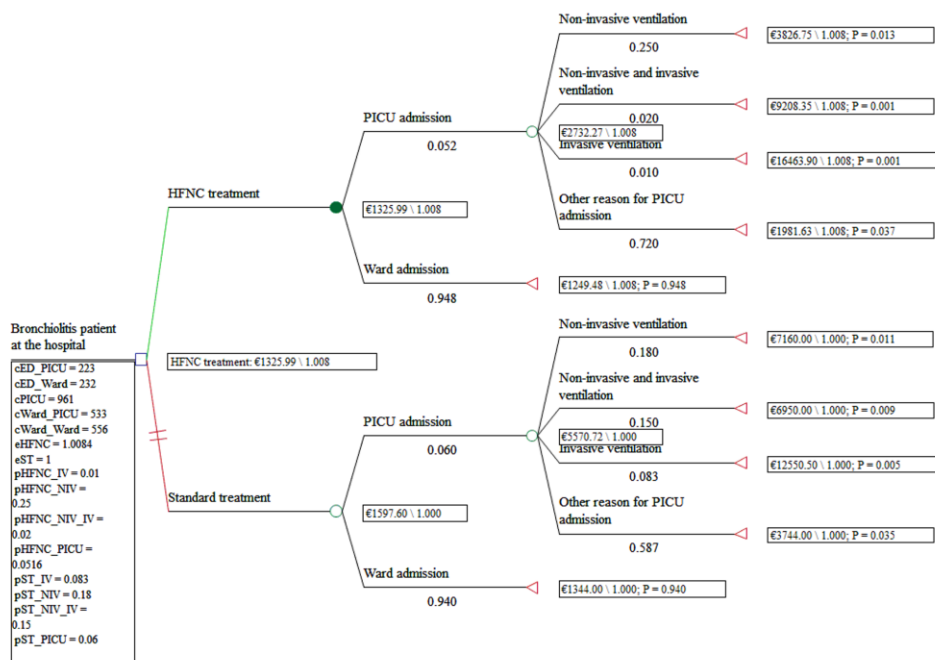
**Figure 10.** The outcome for Model Two (original article II).

The ΔC was €-272 and varied between -235 and -284, and the ΔE was 0.0084 when P was 0.0516. Because of the negative value, the ICER is not presented.

HFOT remained more cost-effective in comparison to LFOT in all sensitivity analyses in Model Two. In contrast, in the worst-case scenarios HFOT lost its dominance. HFOT was more expensive in comparison to LFOT in all three worst-case scenarios: €1,788 compared to €1,704 in worst-case scenario one, €1,875 compared to €1,204 in worst-case scenario two, and €2,524 compared to €1,790 in worst-case scenario three.

## 5.4    Cost-effectiveness of the hypertonic saline inhalations (III)

For outpatient setting analyses, we identified seven studies that included 951 infants with bronchiolitis. In the subgroup analyses, the risk of hospitalisation in the ED did not differ with statistical significance (Figure 11). However, in the overall analysis, the risk of hospitalisation was lower in the HS inhalation group in comparison to the controls, with the RR being 0.80 (95%CI 0.67 to 0.96), and heterogeneity was not important ($I^2$ 2%). The mean hospitalisation rates, in the overall analysis, were 24.7% for HS inhalations and 32.6% for controls. The effectiveness was 1.24, which means a 24% reduction in the hospitalisation rate.
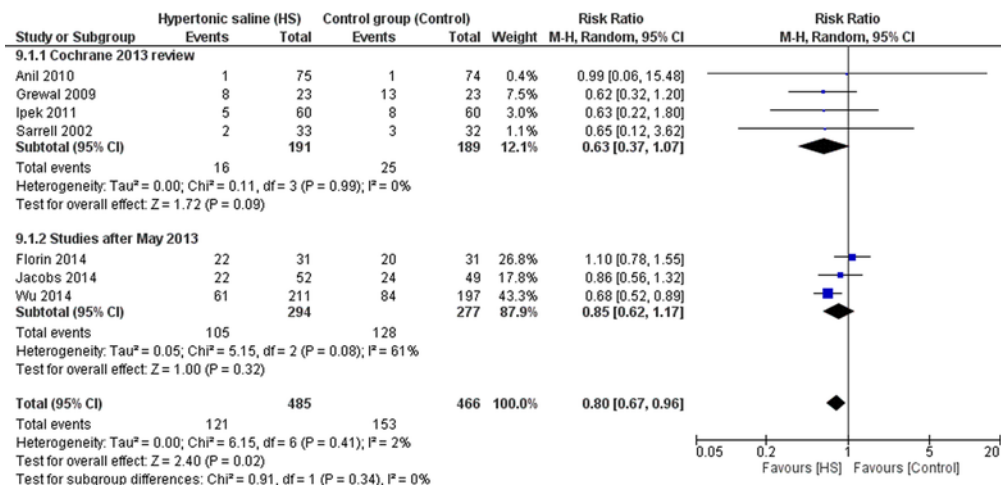


**Figure 11.** The meta-analysis on the hospitalisation risk of infants with bronchiolitis treated with hypertonic saline inhalations, compared to controls. The figure presents first the results of the 2013 Cochrane review, and then the results of the studies published after it, and last the combined results of all studies (original article III).

The expected costs per patient were €816 for HS inhalations and €969 for controls when we used the results of the overall analysis in a decision tree. The ΔC was €-153 and the ΔE was 0.24. Because of the negative value, the ICER is not presented.

For inpatient setting analyses, we identified 14 studies that included 1,694 infants with bronchiolitis. In the subgroup analyses, the LOS in hospital was significantly shorter for HS inhalation groups in the studies included in the 2013 Cochrane review (MD -1.15, 95%CI -1.49 to -0.82). In contrast, in the subgroup of later studies not included in the Cochrane review, there was no statistically significant difference in the LOS (MD -0.01, 95%CI -0.30 to 0.28) (Figure 12).

In the overall analysis, the LOS in hospital was shorter for HS inhalations (3.7 days) than for controls (4.3 days). The mean difference was -0.55 days (95%CI -0.96 to -0.15) and heterogeneity was considerable ($I^2$ 82%) (Figure 12). The effectiveness was 1.13, which means a 13-hour reduction in the LOS in hospital.



| Study or Subgroup | Hypertonic saline (HS) | | | Control group (Control) | | | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Total | Mean | SD | Total | | |
| 8.3.1 Cochrane 2013 review | | | | | | | | |
| Kuzik 2007 | 2.6 | 1.9 | 47 | 3.5 | 2.9 | 49 | 6.2% | -0.90 [-1.88, 0.08] |
| Luo 2010 | 6 | 1.2 | 50 | 7.4 | 1.5 | 43 | 8.2% | -1.40 [-1.96, -0.84] |
| Luo 2011 | 4.8 | 1.2 | 57 | 6.4 | 1.4 | 55 | 8.6% | -1.60 [-2.08, -1.12] |
| Mandelberg 2003 | 3 | 1.2 | 27 | 4 | 1.9 | 25 | 6.7% | -1.00 [-1.87, -0.13] |
| Miraglia 2012 | 4.9 | 1.3 | 52 | 5.6 | 1.6 | 54 | 8.3% | -0.70 [-1.25, -0.15] |
| Tal 2006 | 2.6 | 1.4 | 21 | 3.5 | 1.7 | 20 | 6.3% | -0.90 [-1.86, 0.06] |
| Subtotal (95% CI) | | | 254 | | | 246 | 44.3% | -1.15 [-1.49, -0.82] |
| Heterogeneity: Tau² = 0.05; Chi² = 7.18, df = 5 (P = 0.21); I² = 30% | | | | | | | | |
| Test for overall effect: Z = 6.83 (P < 0.00001) | | | | | | | | |
| | | | | | | | | |
| 8.3.2 Studies after May 2013 | | | | | | | | |
| Everard 2014 | 4.19 | 3.2 | 142 | 4.22 | 3.52 | 149 | 7.2% | -0.03 [-0.80, 0.74] |
| Flores 2016 | 5.6 | 2.3 | 33 | 5.4 | 2.1 | 35 | 5.9% | 0.20 [-0.85, 1.25] |
| Nenna 2014 | 4.1 | 1.2 | 22 | 4.8 | 1.5 | 20 | 6.9% | -0.70 [-1.53, 0.13] |
| Ojha 2014 | 1.87 | 0.96 | 28 | 1.82 | 1.18 | 31 | 8.3% | 0.05 [-0.50, 0.60] |
| Sharma 2013 | 2.65 | 0.98 | 125 | 2.66 | 0.93 | 123 | 9.5% | -0.01 [-0.25, 0.23] |
| Teunissen 2014 | 3.03 | 1.95 | 167 | 2.47 | 1.6 | 80 | 8.7% | 0.56 [0.10, 1.02] |
| Tinsa 2014 | 3.54 | 1.83 | 68 | 4.48 | 3.81 | 26 | 4.1% | -0.94 [-2.47, 0.59] |
| Wu 2014 | 3.16 | 2.11 | 61 | 3.92 | 5.24 | 84 | 5.1% | -0.76 [-2.00, 0.48] |
| Subtotal (95% CI) | | | 646 | | | 548 | 55.7% | -0.01 [-0.30, 0.28] |
| Heterogeneity: Tau² = 0.06; Chi² = 11.47, df = 7 (P = 0.12); I² = 39% | | | | | | | | |
| Test for overall effect: Z = 0.07 (P = 0.95) | | | | | | | | |
| | | | | | | | | |
| Total (95% CI) | | | 900 | | | 794 | 100.0% | -0.55 [-0.96, -0.15] |
| Heterogeneity: Tau² = 0.44; Chi² = 73.83, df = 13 (P < 0.00001); I² = 82% | | | | | | | | |
| Test for overall effect: Z = 2.69 (P = 0.007) | | | | | | | | |
| Test for subgroup differences: Chi² = 25.77, df = 1 (P < 0.00001), I² = 96.1% | | | | | | | | |

Favours [HS]  Favours [Control]

**Figure 12.** The meta-analysis on the length of stay in hospital for infants with bronchiolitis treated with hypertonic saline inhalations in comparison to controls. The figure first presents the results of the 2013 Cochrane review, and then the results of the studies published subsequently and, last, the combined results of all the studies (original article III).

The expected costs per treatment episode were €2,600 for HS inhalations and €2,890 for controls, when we used the results of the overall analysis in the decision tree. The ΔC was €-290 and the ΔE was 0.13. Because of the negative value, the ICER is not presented.

For sensitivity analyses, we applied different hospitalisation rates or LOS in hospital, and different cost values (lower and upper limits of 95%CI). The expected hospitalisation costs per patient varied between €352 and €1,883 for HS inhalations, and between €352 and €1,757 for controls in outpatient analyses. Additionally, the expected hospitalisation costs per treatment episode varied between €1,481 and €3,769 for HS inhalations, and between €1,457 and €3,658 for controls, in inpatient analyses.

In the end, the expected costs for HS inhalations were both less and more, when compared to expected costs of controls.

## 5.5 Effectiveness of the hypertonic saline inhalations in cumulative meta-analysis (IV)

The literature search conducted up to the 20th of June 2017, identified 398 studies and, after duplicates were removed, yielded a total of 200 studies. We selected 75/200 based on the title, 32/75 by looking at the abstract and 25/32 after reading the full paper (Figure 13).
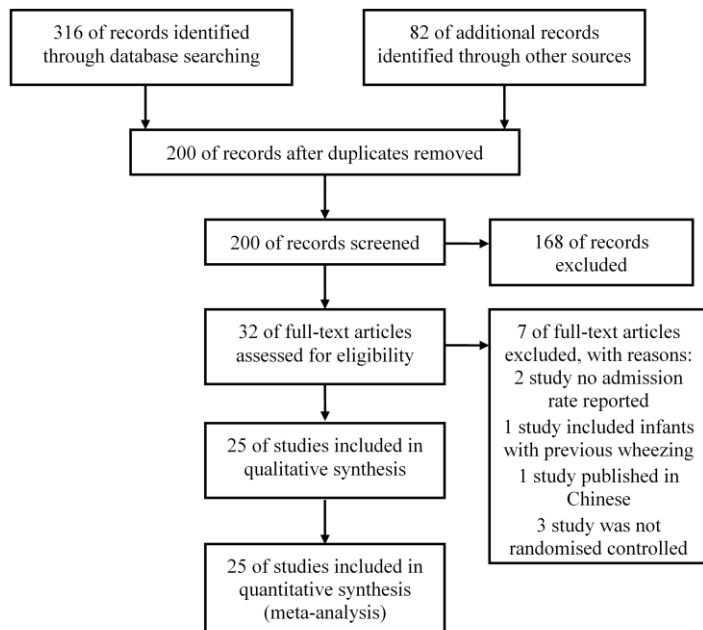


**Figure 13.** Flow diagram of the study selection for the cumulative meta-analysis (original article IV).

The 25 studies selected were heterogeneous. They were done in 14 different countries and published over a period of 13 years, from 2003 to 2017. The definition of bronchiolitis varied, and the upper age limit in particular varied greatly, from 12 to 24 months. Moreover, the average age of participating infants varied between two and 9.5 months. In addition, the concentration of the HS solution, dose, scheduled administration and adjunct therapy varied considerably between the studies (Appendix table).

The risk of bias was evaluated for each study at the study level. In most studies, the risk of bias was low, and in eight studies, it was very low. However, in three studies the risk of bias was assessed to be considerable (Table 6).

**Table 6.** The risk of bias evaluation of the original studies included in the cumulative meta-analysis (original article IV).

| Study | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
|---|---|---|---|---|---|---|---|
| Al-Ansari 2010 | + | + | + | ? | ? | + | ? |
| Angoulvant 2017 | + | + | + | + | + | + | + |
| Anil 2010 | + | + | + | + | ? | + | + |
| Everard 2014 | + | + | - | - | ? | + | + |
| Flores 2016 | + | + | + | + | ? | + | + |
| Florin 2014 | + | + | + | + | + | + | + |
| Grewal 2009 | + | + | + | + | + | + | + |
| Ipek 2011 | ? | ? | ? | ? | ? | + | ? |
| Jacobs 2014 | + | + | + | + | + | + | + |
| Khanal 2015 | + | + | + | + | + | + | ? |
| Kuzik 2007 | + | ? | + | + | + | + | + |
| Köse 2016 | ? | ? | ? | ? | + | + | ? |
| Luo 2010 | ? | ? | + | + | + | + | ? |
| Luo 2011 | + | + | + | + | - | + | ? |
| Mandelberg 2003 | ? | ? | + | + | ? | + | ? |
| Mahes Kumar 2013 | + | ? | ? | ? | + | + | ? |
| Miraglia 2012 | + | ? | + | + | ? | + | ? |
| Nenna 2014 | + | ? | + | + | ? | + | + |
| Ojha 2014 | + | + | + | + | + | + | + |
| Pandit 2013 | + | + | + | + | + | + | + |
| Sharma 2013 | + | + | + | + | ? | + | + |
| Tal 2006 | ? | ? | + | + | ? | + | ? |
| Teunissen 2014 | + | + | + | + | + | + | + |
| Tinsa 2014 | + | + | + | + | ? | + | ? |
| Wu 2014 | + | + | + | + | + | + | + |

(Al-Ansari et al. 2010; Anil et al. 2010; Everard et al. 2014; Flores, Mendes, Neto 2016; Florin et al. 2014; Grewal et al. 2009; Ipek et al. 2011; Jacobs et al. 2014; Khanal et al. 2015; Kose et al. 2016; Kuzik et al. 2007; Luo et al. 2010; Luo et al. 2011; Mahesh Kumar et al. 2013; Mandelberg et al. 2003; Miraglia Del Giudice et al. 2012; Nenna et al. 2014; Ojha et al. 2014; Pandit, Dhawan,

Thakur 2013; Sharma, Gupta, Rafik 2013; Tal et al. 2006; Teunissen et al. 2014; Tinsa et al. 2014; Wu et al. 2014)

For inpatient setting analyses, we identified 18 studies that included 2,102 infants with bronchiolitis. In the overall analysis, the LOS in hospital was shorter with HS inhalations. The cumulative MD was -0.481 days (95%CI -0.750 to -0.212) and the heterogeneity was substantial ($I^2$ 66.4%) (Figure 14). Since 2013, the MD has become closer to the null, indicating a decrease in the effectiveness of HS inhalations.
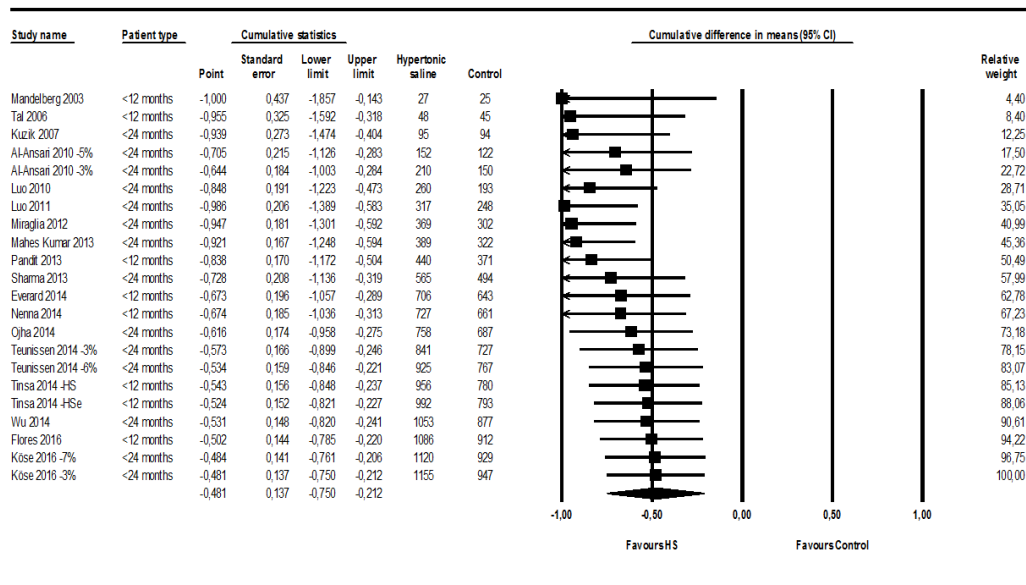


**Figure 14.** The cumulative meta-analysis on the length of stay in hospital for infants with bronchiolitis who were treated with hypertonic saline inhalations in comparison to controls (original article IV).

Any significant publication bias was not seen in the funnel plot (Figure 15), even though it was not a classical funnel. The Egger´s test (2-tailed p=0.361) did not reveal any significant asymmetry between the studies.
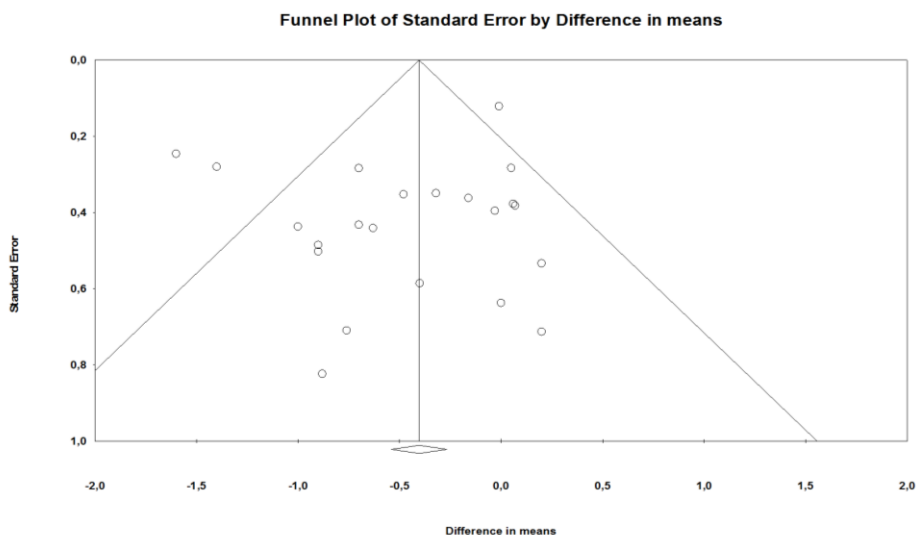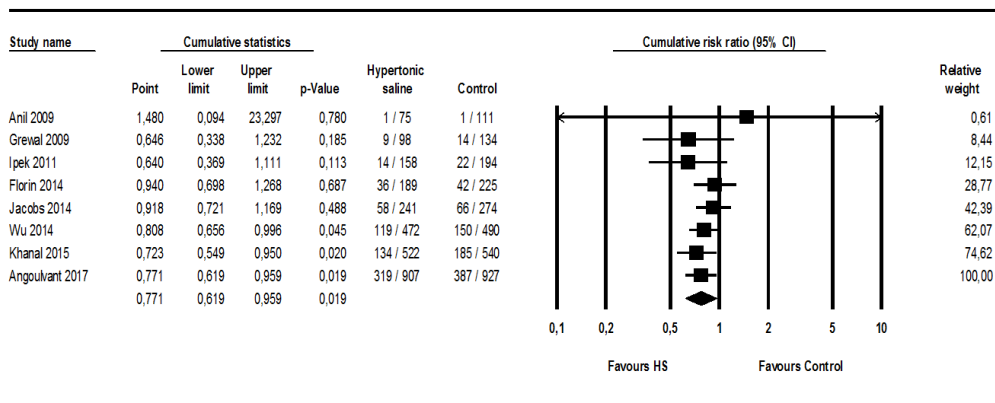
**Figure 15.** The funnel plot of the studies included in the cumulative meta-analysis on the length of stay in hospital for infants with bronchiolitis that were treated with hypertonic saline inhalations in comparison to controls (original article IV).

Due to the heterogeneity, we performed subgroup analyses and noticed that the cumulative MD was -0.408 days (95%CI -0.733 to -0.083), and that there was no heterogeneity ($I^2$ 0%) in the first subgroup, including the studies with the upper age limit of 12 months. The heterogeneity increased considerably ($I^2$ 76.7%) in the second subgroup that included the studies where the upper age limit was 24 months (without the studies included in the first subgroup), while the cumulative MD was similar at -0.507 days (95%CI -0.866 to -0.147).

We performed sensitivity analyses and removed one study at a time from the meta-analysis. This did not affect the results significantly. In another sensitivity analysis, we moved one study (Teunissen et al. 2014) from the second subgroup to the first subgroup, finding a better fit in the average age of participants. In this sensitivity analysis, HS did not shorten the LOS in hospital in a statistically significant amount. Cumulative MD was -0.277 days (95%CI -0.554 to 0.0) and the heterogeneity was not important ($I^2$ 0%).

We evaluated four studies that included 549 infants, which had a very low risk of bias in inpatient setting. In the secondary analysis with these four studies, the HS inhalations did not shorten the LOS in hospital. Cumulative MD was 0.034 (95%CI -0.361 to 0.293, $I^2$ 0%), and thus the heterogeneity was not important, and the result was not statistically significant.

For outpatient setting analyses, we identified eight studies that included 1,834 infants with bronchiolitis. In the overall analysis, the risk of hospitalisation was significantly lower in the case of HS inhalations. The cumulative RR was 0.771 (95%CI 0.619 to 0.959) and the heterogeneity was substantial ($I^2$ 55.8%) (Figure 16).



| Study name | Cumulative statistics | | | | | | Cumulative risk ratio (95% CI) | Relative weight |
|---|---|---|---|---|---|---|---|---|
| | Point | Lower limit | Upper limit | p-Value | Hypertonic saline | Control | | |
| Anil 2009 | 1,480 | 0,094 | 23,297 | 0,780 | 1 / 75 | 1 / 111 | | 0,61 |
| Grewal 2009 | 0,646 | 0,338 | 1,232 | 0,185 | 9 / 98 | 14 / 134 | | 8,44 |
| Ipek 2011 | 0,640 | 0,369 | 1,111 | 0,113 | 14 / 158 | 22 / 194 | | 12,15 |
| Florin 2014 | 0,940 | 0,698 | 1,268 | 0,687 | 36 / 189 | 42 / 225 | | 28,77 |
| Jacobs 2014 | 0,918 | 0,721 | 1,169 | 0,488 | 58 / 241 | 66 / 274 | | 42,39 |
| Wu 2014 | 0,808 | 0,656 | 0,996 | 0,045 | 119 / 472 | 150 / 490 | | 62,07 |
| Khanal 2015 | 0,723 | 0,549 | 0,950 | 0,020 | 134 / 522 | 185 / 540 | | 74,62 |
| Angoulvant 2017 | 0,771 | 0,619 | 0,959 | 0,019 | 319 / 907 | 387 / 927 | | 100,00 |
| | 0,771 | 0,619 | 0,959 | 0,019 | | | | |

Favours HS    Favours Control

**Figure 16.** The cumulative meta-analysis on the hospitalisation risk for infants with bronchiolitis that were treated with hypertonic saline inhalations in comparison to controls (original article IV).

For subgroup analyses, we found two studies with the upper age limit of 12 months and the cumulative RR did not have a statistical significance, being 0.863 (95%CI 0.645 to 1.153) and the heterogeneity was not important ($I^2$ 25%). In the second subgroup analysis, with the studies where the upper age limit was 24 months (and not including the studies found in the first subgroup), the cumulative RR was not statistically significant, being 0.736 (95%CI 0.539 to 1.004), but the heterogeneity remained substantial ($I^2$ 57.2%).

We then performed sensitivity analyses by removing one study at a time from the meta-analysis. When a large study that included 447 infants was removed, the cumulative RR was not statistically significant, being 0.790 (95%CI 0.612 to 1.021), and the heterogeneity was substantial ($I^2$ 53.9%). The removal of other studies did not significantly affect the results.

We considered six studies that included 1,528 infants to have a very low risk of bias in the outpatient setting. In the secondary analysis with these six studies, the cumulative RR was 0.770 (95%CI 0.607 to 0.976) and the heterogeneity was substantial ($I^2$ 67.5%).

# 6 DISCUSSION

## 6.1 Hospitalisation costs from 2000 to 2012

In the present study, the average hospitalisation costs for infant bronchiolitis were over four times higher if intensive care was needed when compared to the treatment on the ward only. Additionally, the LOS on the ward was also higher if patients were treated in the PICU in comparison to those treated on the ward only. The estimated direct hospitalisation costs were between €1.5 million and €4.4 million annually in Finland, depending on the severity of the epidemic in a year.

The higher hospitalisation costs for PICU treated patients were accounted for through a longer LOS in the PICU, and a longer total LOS in the hospital. However, the LOS in the PICU and the hospitalisation year were the only independently significant factors associated with higher hospitalisation costs in PICU treated infants in multivariate analysis. We did not find any consistent trends in the hospitalisation costs per patient or per patient per day during the study period, but annual numbers and, hence, the mean annual hospitalisation costs, varied substantially.

In multivariate linear regression analysis, the coefficient of determination was 37.3%. This means that 62.7% of the variations in hospitalisation costs were accounted for through factors other than those we included in the analysis. In Finland, the social and economic class distinctions are rather low and, consequently, it is unlikely that including those parameters would have made the analysis model substantially better. Instead, parental smoking, especially maternal smoking, during pregnancy is a well-known risk factor for severe bronchiolitis (Carroll et al. 2008), and using that factor would have improved the analysis model. Unfortunately, it was not possible to obtain the parental smoking data from the hospital records through retrospective data collection.

Other risk factors for severe bronchiolitis are being under three months of age on admission and preterm birth (Carroll et al. 2008; Hervas et al. 2012). In this study, the mean gestational age was lower in the PICU treated infants than the controls, and nearly 50% of those were born preterm in comparison to 12% of controls and 4.2% of the overall Finnish population (National Institute of Health

and Welfare, Finland). However, the age on admission was not associated with higher hospitalisation costs with PICU treated infants, while the gestational age was associated with higher costs only suggestively.

The total direct hospitalisation costs per annum for infant bronchiolitis were $545 million in the USA in 2009 (Hasegawa et al. 2013b), and the mean hospitalisation costs per patient varied between $3,208 and $6,191 depending on comorbidities in 2002 (Pelletier, Mansbach, Camargo 2006). Those costs from the USA were higher, in relation to the population, than the estimated annual hospitalisation costs and mean costs per patient in this study. Additionally, the mean hospitalisation costs for RSV infections treated on the ward were €2,772 in Germany in 2002 (Ehlken et al. 2005) in comparison to €1,587 in this present study.

The other studies from the USA found that an RSV infection in infancy, such as infant bronchiolitis, led to higher health care use, as well as higher costs, during the subsequent year in comparison to those infants without an RSV infection (Palmer et al. 2011). The marginal costs were up to $34,132 among inpatient preterm infants with an RSV infection, compared to those infants without an RSV infection (Shi et al. 2011).

However, comparing hospitalisation costs between various countries and in different years is difficult, because different patient and cost data were used in published studies. The differences between the mean hospitalisation costs can partially be explained by the differences in general price levels in different countries, and by differences in the ways those countries organise and fund health care.

To decrease the hospitalisation costs of bronchiolitis, the admission rate to the PICU, the LOS in the PICU and/ or the LOS in the hospital need to be decreased. In a French study, the use of nCPAP as primary respiratory support instead of mechanical ventilation decreased the admission rate to the PICU and the LOS in hospital, and led to lower hospitalisation costs (Essouri et al. 2014). In addition, the use of HFOT may decrease the admission rate to the PICU (McKiernan et al. 2010; Schibler et al. 2011). On the other hand, the recently published retrospective study from the USA, found that a higher adherence to standardised clinical processes of care in infant bronchiolitis was associated with decreased hospitalisation costs and shorter stays both in the ED and on the ward (Bryan et al. 2017).

## 6.2　　　Cost-effectiveness of the high flow oxygen therapy

HFOT was more effective and less expensive than LFOT in infant bronchiolitis if supportive oxygen was needed in this theoretical model. Both the decreased cost and increased effectiveness of HFOT were mainly due to the lower PICU admission rate.

In these analyses, we estimated the effectiveness of HFOT as the way to reduce the PICU admission rates. HFOT is a safe and well-tolerated treatment, and thus it can be carried out on the ward (Bressan et al. 2013; Hilliard et al. 2012; Mayfield et al. 2014). For that reason, we presumed that the PICU admission rate decreased as much as the use of HFOT reduced the intubation rate. However, our effectiveness estimates were based on retrospective studies with pre- and post-HFOT analyses, and that kind of historical data are not very reliable.

HFOT retained dominance in sensitivity analyses, even with the lowest effectiveness levels. In contrast, HFOT lost dominance in worst-case scenario analyses. Those scenarios are extremely rare and the dominance was lost because of higher costs. Higher costs are acceptable if the effectiveness is sufficient and the more expensive treatment provides more benefits (Rawlins 2016).

HFOT provided beneficial physiological effects in infant bronchiolitis in observational studies. Two studies demonstrated the significant increases in oxygen saturation and decreases in respiratory rate when HFOT was used (Bressan et al. 2013; Hough, Pham, Schibler 2014). Additionally, two other studies demonstrated that the work of breathing decreased when HFOT was used with the flow rate of 7L/min or 2L/min/kg (Milesi et al. 2013; Pham et al. 2015).

In an RCT that included 19 infants, the median oxygen saturation was higher in the HFOT group than in the LFOT group during the first 12 hours (Hilliard et al. 2012). Another RCT included 202 infants under 24 months of age with bronchiolitis, and found that the PICU admission rates were equal, but that the infants treated with HFOT had less treatment failures. Two-thirds of the infants with LFOT who experienced treatment failure, got better with HFOT. In addition, those infants treated with HFOT had better comfort, feeding and sleep scores. The authors concluded that HFOT might be useful as a rescue therapy and reduce the proportion of children requiring intensive care. (Kepreotes et al. 2017)

Tampere University Hospital provides inpatient care to approximately 6,000 infants under 12 months of age. Theoretically, if all infants with bronchiolitis who need oxygen support were treated with HFOT instead of LFOT, the annual savings in direct hospitalisation costs would be between €16,320 and €48,960

depending on the extent of the epidemic in a given year. This calculation is based on average total hospitalisation costs and the lowest effectiveness used in this decision analysis. The HFOT device costs approximately €4,900 and, hence, the annual savings might cover the acquisition of three to ten new devices. RSV epidemics are usually short and intensive, and consequently a limited number of HFOT devices may be the limiting factor when it comes to using HFOT during the peak of the epidemic.

## 6.3    Cost-effectiveness of the hypertonic saline inhalations

The cost-effectiveness of HS inhalations remains unclear in infant bronchiolitis in comparison to NS inhalations, or to standard care without inhalations. The expected costs per patient and per treatment episode are slightly lower for HS inhalations compared to controls. On the other hand, the effectiveness of HS inhalations was low and has decreased over the time. Therefore, the limitation of HS inhalations in infant bronchiolitis is its low effectiveness, rather than the costs.

The expected costs per patient for HS inhalations were lower when HS inhalations reduced the hospitalisation rate. This present meta-analysis included seven studies which showed a risk ratio of 0.80 for hospitalisation. The mean reduction in the hospitalisation rate was 24%, and this indicates €146 ($199) savings per patient in this decision analysis. Only one study of those included in this meta-analysis demonstrated an independently significant (13.7%) reduction in hospitalisation rates between infants treated with HS vs NS inhalations (Wu et al. 2014).

The expected costs per treatment episode with HS inhalations are lower when HS inhalations reduce the LOS in hospital, the PICU admission rate or the LOS in the PICU. The four studies included in the 2013 Cochrane review, reported a statistically significant reduction of the LOS in hospital (Luo et al. 2010; Luo et al. 2011; Mandelberg and Amirav 2010b; Miraglia Del Giudice et al. 2012), but none of the studies published after that review reported such reduction. The published studies have not documented significant reductions in the PICU admission rate, nor in the LOS in the PICU.

This present meta-analysis included 14 studies and showed a 13-hour mean reduction in the LOS in hospital, which may not implicate true savings. In many countries, including Finland, hospital invoicing is based on daily prices or mean

prices for diagnosis-related groups, which means that even a statistically significant LOS in hospital reduction in hours would not affect the realised costs.

Essentially, the effectiveness of HS inhalations is more or less controversial. In two recently published meta-analyses, the authors left out some studies to control the heterogeneity, and the resulting mean difference in the LOS was -0.22 (95%CI -0.54 to 0.10) (Heikkila and Korppi 2016) and -0.26 (95%CI -0.82 to 0.30)(Overmann and Florin 2016). These differences are not clinically, statistically or economically significant.

## 6.4 Effectiveness estimates in cost-effectiveness analyses

In both HFOT and HS decision analyses, we estimated the effectiveness of the treatment on the basis of previously published studies, in which the effectiveness estimation was in turn based on reported measurements. Due to this factor, we could not apply the best effectiveness measurements.

For HFOT analyses, the effectiveness was evaluated in form of reduction in the PICU admission rates in the inpatient setting, and for HS analyses the effectiveness was evaluated in form of reduction in the hospital admission rates in the outpatient setting, or as a reduction of the LOS in hospital in the inpatient setting. Other, more reliable, effectiveness estimates were not available.

Bronchiolitis, during the time when an infant is diseased, affects the family through sleep disturbances, transportation problems and an inability to attend usual activities and appointments (Ehlken et al. 2005). Taking care of a diseased child requires more of the parents` time than usual (Lambert et al. 2008; Leader and Kohlhase 2003). This type of time loss and other losses to the factors associated with the quality of life could not be evaluated in this thesis.

Earlier studies have described that hospitalising infants for bronchiolitis reduced the health-related quality of life. In three studies, parents filled the Infant Toddler Quality of Life Questionnaire two to nine months after hospitalisation. In all these studies, the general health had decreased significantly in those with bronchiolitis compared to those without bronchiolitis in infancy, and the severity of bronchiolitis was associated to a strong reduction in health related quality of life (Rolfsjord et al. 2015; Rolfsjord et al. 2016; Spuijbroek et al. 2011). Another study found that health related quality of life measured by TNO AZL Child Quality of Life Questionnaire, had decreased three years after hospitalisation, not only for the lung domain, but also for the gastrointestinal and sleep domain (Bont

et al. 2004). A Finnish prospective cohort study reported impaired health related quality of life, as measured by the St. George´s Respiratory Questionnaire, even in the adulthood of those who were hospitalised for bronchiolitis in infancy (Backman et al. 2014). However, these disease-specific quality of life questionnaires are not suitable for use in cost-effectiveness or cost-utility studies in general.

Some studies have reported lower clinical severity scores for infants with bronchiolitis if HS inhalations were used. However, in this thesis, the clinical severity score was not chosen as an effectiveness estimate, because the most effectiveness was gained in the second or third day in hospital (Zhang et al. 2015) and these infants got better within three days even if only standard supportive care was given (Cornfield 2014).

In addition, no substantial differences in the quality-of-life dimension were reported in a British study that included 54 infants treated with HS inhalations and 49 controls (Everard et al. 2014). In the 2015 British Health Technology Assessment report, HS inhalations were not effective when assessed by quality-adjusted life years, in comparison to standard treatment without inhalations, but this quality measure was only assessed for the duration of hospitalisation (Everard et al. 2015).

An interesting question is whether HFOT can influence the quality of life in infants hospitalised for bronchiolitis and, furthermore, the life of their families. Currently available indirect evidence suggests that such beneficial influence could be possible. HFOT seems to have beneficial effects on breathing physiology (Bressan et al. 2013; Hough, Pham, Schibler 2014), clinical scores (Abboud et al. 2012) and the hospitalised infants´ general condition (Kepreotes et al. 2017; Milani et al. 2016), and may reduce the need for more invasive procedures (Kepreotes et al. 2017) and intensive care (Mayfield et al. 2014). However, direct prospective data are lacking.

## 6.5 Effectiveness of the hypertonic saline inhalations in cumulative meta-analysis

The cumulative MD in the LOS in hospital was approximately 12 hours between infants treated with HS inhalations in comparison to controls. The MD has decreased over the time, and the trend towards the null point continues. This means that the results of earlier studies that demonstrate HS inhalations to be

more effective than NS inhalations, maybe due to publication bias of the early 21th century. The cumulative RR for hospitalisation was 0.771 between infants treated with HS inhalations in comparison to controls treated in the outpatient setting. This was not dependent on the time when the study was done.

The heterogeneities between the studies, measured by the Higgin´s $I^2$ value, were substantial or considerable in both the overall and subgroup analyses, including the studies that defined 24 months of age as the upper age limit for bronchiolitis. In contrast, in the subgroup analyses with the studies that defined 12 months of age as the upper age limit for bronchiolitis, the heterogeneity was not significant.

In the inpatient setting, the higher heterogeneity between the studies can be seen as evidence that the clinical picture of bronchiolitis at over 12 months of age is more heterogeneous. The bronchiolitis causative viruses, the host properties and bronchiolitis as a disease differ depending on age. RSV is the predominant causative agent for bronchiolitis in infants under six months of age, whereas both RSV and rhinovirus are common agents of the disease in infants between six and 12 months of age, with rhinovirus especially being associated with recurrent wheezing. (Korppi, Koponen, Nuolivirta 2012) Furthermore, the phenotypes varied in wheezing illnesses by age and that may affect the response to treatment. At the time of a first respiratory distress caused by a viral LRTI, this dilemma is especially important. (Frey and von Mutius 2009) Most hospitalised infants with bronchiolitis were, irrespective of the selected upper age limits, six months or younger in the studies, which was included in the present cumulative meta-analysis.

In the outpatient setting, the heterogeneity was lower in comparison to that in the inpatient setting. In most studies, the upper age limit was set to 24 months. There are two possible reasons for this low heterogeneity: that 1) the infants included had mild to moderate bronchiolitis treated mainly at home, and that 2) the number of studies was small.

Unfortunately, there is no widely accepted international definition for bronchiolitis (Florin, Plint, Zorc 2016). Therefore, it is challenging to compare individual studies both in inpatient and in outpatient settings. Additionally, the HS concentrations used varied, as well as the administration schedules and adjunct therapies. Because of the heterogeneity of the patients, disease severity, bronchiolitis definitions and other therapies, there are multiple subgroups to be considered in the meta-analysis that compares HS inhalations to controls in infant bronchiolitis.

One meta-analysis reported that HS inhalations decreased the risk of hospitalisation in a subgroup in which viral determination was available and multiple HS inhalations were given, but the selection bias was unclear or high (Zhang et al. 2015). In the inpatient settings, HS inhalations reduced the LOS in hospital compared to NS inhalations only for those who stayed in the hospital more than three days (openMetaAnalysis 2016). Another meta-analysis constructed subgroups by adjunct therapy, and the LOS in hospital was reduced significantly only for those treated with adrenaline (Maguire et al. 2015). Recently, HS inhalations decreased the LOS in hospital significantly for a subgroup of Chinese infants and for a subgroup whose illness duration was balanced (Brooks, Harrison, Ralston 2016).

However, the effectiveness of HS inhalations is the sum of beneficial and non-beneficial effects caused by HS and NS inhalations. Thus far, only one study compared the HS inhalations to standard care without inhalations (SABRE study). No significant differences were found between HS inhalations and standard care in infant bronchiolitis measured via the LOS in hospital or the time by which the patients were ready for discharge. (Everard et al. 2014)

Although most infants with bronchiolitis have tolerated HS inhalations well, some adverse events have been reported. In the SABRE study, one serious adverse event of bradycardia and desaturation during the inhalation was reported, and five mild adverse events were self-corrected bradycardia, desaturation, coughing fit, increased respiratory rate and a chest infection. (Everard et al. 2014) Another multicentre study reported multiple adverse events. Most of them were agitation, rhinorrhoea and coughing, but there were also severe ones such as bronchial obstructions, saturation drops and tachycardia. (Teunissen et al. 2014)

In 2014, The European Respiratory Journal proposed criteria for therapeutic studies in infant bronchiolitis. Bronchiolitis should be defined clearly, the design should be a multicentre double-blind RCT, the intervention should be done with one single drug and the outcomes should be clinically relevant (Barben and Kuehni 2014). The SABRE study (Everard et al. 2014) was a multicentre RCT, unfortunately, but understandably, open and it included 141 cases and 149 controls under 12 months of age. HS inhalations without adjunct therapy were compared to standard care with no inhalations. Therefore, control infants were not exposed to harmful effects, such as interruptions due to NS inhalations. HS inhalations were not effective in comparison to standard care. (Everard et al. 2014) The evidence of the uselessness of HS in infant bronchiolitis is strong based on the SABRE study, but the results should the repeated.

## 6.6 Methodological aspects of the study

### 6.6.1 Strengths of the study

This thesis consists of one cost analysis, two cost-effectiveness analyses made using decision tree and one cumulative meta-analysis. The viewpoint of the thesis is that of the health care provider, with a focus on special health care. The cost data consist of the direct hospitalisation charges based on daily municipal billing, but family-related costs such as transport and loss of time or other productive losses were not considered. Bronchiolitis, as a disease, is an acute LRTI without any common sequels or need of controls in an outpatient clinic. For these reasons, the hospitalisation costs are the most important.

Most infants with bronchiolitis are young, and for this thesis the mean age of those treated in the PICU was three months, and five months for those in controls who were not treated in the PICU. It is usual for one of the parents to participate in the infant´s care in the hospital for the majority of its stay. Typically, at the time of the hospitalisation the mother is on maternity leave, so that the losses arising from work absence or productive losses remain minor. However, providing adequate childcare for the infant's siblings causes difficulties and time losses for the family. In addition, the hospitalisation causes anxiety and worries the families. In this thesis, we could neither evaluate the number of siblings, nor the time used for the infant´s care in the hospital, because of the retrospective research frame.

Commonly, the distribution of costs is skewed to the lower costs, as it was also in this data. This means, that the mean costs are not equivalent to the costs of an average patient (Akobundu et al. 2006). However, mean costs are useful when evaluating the costs at the population level as we have done here. The costs based on municipal billing, which we used, are more or less mean costs by themselves. They describe the costs at the level of macro costing, but are not similar to the costs caused by the resources used. On the other hand, the costs based on municipal billing described the true transference of money.

The way in which the data was collected is one of the strengths of this thesis. We collected the patient data from the electronic files of the Tampere University Hospital with a wide scale of diagnosis numbers, and then we verified the diagnosis of bronchiolitis via the details from the patient records. We identified every bronchiolitis patient treated in the PICU between the years 2000 and 2012.

Then we collected the cost data concerning the treatment period for bronchiolitis separately for every patient.

Additionally, we selected to use the retrospective case-control research frame to find as many infants with bronchiolitis treated in the PICU as possible. The study design gave reliable data, because the treatment of bronchiolitis had remained nearly the same during the data collection time-frame. We collected the comparable information regarding the costs in the ED, on the ward and in the PICU.

For cost-effectiveness analyses by decision tree, we used the hospitalisation costs that were based on real patients collected over a period of 13 years, as well as on the actual daily municipal billing. We neither estimated the costs, nor used average costs per treatment day in our hospital. The decision trees made it possible to combine various data available, including costs and effectiveness data from different sources and for different outcomes into one decision tree. In addition, the reliability of the results can be evaluated via sensitivity analyses. Even though the data of the hospitalisation costs were based on a study made in only a single centre, the differences between the expected costs were more important than exact monetary costs. Furthermore, the results of the newest trials were applied as effectiveness estimates in the analyses.

## 6.6.2    Limitations of the study

This thesis has some limitations. One limitation is the confined viewpoint. The cost data included the direct hospitalisation charges only. The costs of primary care, family or society were not evaluated. Furthermore, these evaluated costs were not exactly actual costs, because the hospital did not follow real market prices. However, bronchiolitis is a short-term disease, and so the viewpoint of the hospital is reasonable. We decided to carry out this cost analysis, because we considered it important to describe the hospitalisation costs of bronchiolitis, which were then included in the modelled cost-effectiveness studies.

The effectiveness outcomes were based on previously published studies, as discussed above, but some other outcomes might have been more useful. We used the hospital admission rate, the PICU admission rate and the LOS in hospital or in the PICU as the effectiveness outcomes. However, it should be noted that the available facilities at the wards, and thus the indications of the PICU treatment, vary between different hospitals.

The frame of this thesis, the cost of bronchiolitis hospitalisation, was a retrospective evaluation with a focus on special care only. On the other hand, we collected data on all infants treated in the intensive care unit for bronchiolitis during the 13-year study period, which is the only way to collect data large enough in one centre within a reasonable time-frame and use of resources. Additionally, data sources we used were the electronic files of the Tampere University Hospital. Of course, human error can happen, but, generally, the data details included in those files were reliable.

The two cost-effectiveness analysis studies were modelling studies. We connected the data from various sources and did numerous estimates. The data sources, the observational studies for effectiveness data and the single hospital focus for costs, were all rated as good evidence for decision-making (Mullins et al. 2014). We used only deterministic sensitivity analysis, not probabilistic sensitivity analysis. However, we did many different sensitivity analyses and used one-way and n-way sensitivity analyses as well as scenario analyses. The positive results of the HFOT study were suggestive, and need to be confirmed by a prospective cost-effectiveness analyses. At the same time, the results of the HS study were more reliable, because less estimation needed to be done. The cumulative meta-analysis, which we did after the HS decision-analytic modelling, actually confirmed that the effectiveness of HS inhalations is marginal, or even absent, in infant bronchiolitis when compared to NS inhalations and to standard therapy without inhalations especially.

# 7   CONCLUSIONS

The total mean hospitalisation costs of bronchiolitis were €8,061 for inpatient treatment if intensive care was needed, €1,834 for inpatient treatment when intensive care was not needed, and €359 for ED treatment only. The higher costs were correlated strongly with the total LOS in hospital and the LOS in PICU, and weakly with the gestational age and age on admission. However, in the multivariate linear regression analysis, the treatment year and the LOS in PICU were the only independently significant factors associated with higher costs. Nevertheless, no constant decreases or increases were found by the year in the mean costs per treatment episode, or in the mean costs per treatment day.

High flow oxygen therapy was cost-effective compared to low flow oxygen therapy in infant bronchiolitis in the theoretic model constructed for this thesis. HFOT was both more effective and less expensive. The modelling suggests that all infants with bronchiolitis who need oxygen support during hospitalisation, should be treated with HFOT instead of LFOT. However, the estimated reductions in the admission rate to the PICU were based on retrospective studies. Therefore, prospective randomised controlled studies are urgently needed to confirm the effectiveness of HFOT, as well as the indications, benefits and cost-effectiveness of HFOT.

Hypertonic saline inhalations slightly reduced the expected hospitalisation costs for infant bronchiolitis compared to control treatments, but the effectiveness was minor in outpatients and absent in inpatients. In fact, the limitation of HS inhalations in infant bronchiolitis is its low effectiveness, rather than the costs.

The effectiveness of HS inhalations had decreased by the time the studies were done. Since 2014, the cumulative mean difference in the LOS in hospital has been approximately 0.5 days, but the cumulative trend towards the null continues in 2016. The effectiveness of the emergency department measured by the cumulative risk ratio for hospitalisation was 0.771, and no significant trend was seen by the time of this thesis.

In the summary, intensive care is especially expensive and strategies to reduce the need for intensive care are needed. With current knowledge, HFOT impresses and promises a dominant way to treat infants with bronchiolitis when they have

respiratory distress. In contrast, HS inhalations are not as effective that any real savings may be gained, and therefore HS inhalations may not be used routinely anymore for the treatment of infant bronchiolitis.

# 8 ACKNOWLEDGEMENTS

Firstly, I want to express my deepest gratitude to my supervisor, Professor Matti Korppi. Matti, it has been an honour working with you. You have been highly encouraging during this process, and have devoted your time to listen to me and to discuss different items. I have learnt a lot of about scientific reasoning and researching in general from you.

I also want to thank the members of my dissertation committee, Docents Nina Hutri-Kähönen and Olli Lohi, for their expertise, kind advice and interest that they expressed in my work.

I am grateful to Professor Janne Martikainen and Docent Heikki Lukkarinen, the official reviewers of this dissertation. You shared your expertise in a very supportive manner, and your comments and recommendations have made this thesis better.

I warmly thank my co-authors PhD Leena Forma, MD Minna Mecklin and Professor Marjo Renko. It has been a pleasure to work with you. Your comments and work have been important for these manuscripts.

I also want to express my thanks to all those of you who were a part of the same bronchiolitis group, or worked with me at the same time: Minna, Laura, Eero, Sari, Susanna, Paula, Annukka, Riikka and Kirsi. We have shared nice times and conversations together. I also wish to thank Sari for being a substitute, so that I could concentrate on this.

Many of my friends and colleagues have supported me during this process as well. Thank you all for everything, thanks for the conversations, time we spent together and for giving me something else to think about. It was refreshing to do different things with you.

My warmest thanks goes to my family, especially to my dear parents Elvi and Pekka. You have always believed in me and encourage me to try to achieve more, I want to thank you for all of your help. I give thanks, too, to my parents-in-law Leena and Pekka, you have helped us in many everyday tasks and in taking care of Roope, and thus you made it possible for me to do this study.

Dear Mikko, thank you for your support during these years. I am grateful for our lovely son, Roope, who has given more content to our everyday lives. Both of you are incredibly important and beloved to me.

<div style="text-align: right;">

Orivesi, September 2017
Paula Heikkilä

</div>

# 9 REFERENCES

Abboud PA, Roth PJ, Skiles CL, Stolfi A, Rowin ME. 2012. Predictors of failure in infants with viral bronchiolitis treated with high-flow, high-humidity nasal cannula therapy*. Pediatr Crit Care Med 13(6):e343-9.

Ademi Z, Kim H, Zomer E, Reid CM, Hollingsworth B, Liew D. 2013. Overview of pharmacoeconomic modelling methods. Br J Clin Pharmacol 75(4):944-50.

Akenroye AT, Baskin MN, Samnaliev M, Stack AM. 2014. Impact of a bronchiolitis guideline on ED resource use and cost: A segmented time-series analysis. Pediatrics 133(1):e227-34.

Akobundu E, Ju J, Blatt L, Mullins CD. 2006. Cost-of-illness studies : A review of current methods. Pharmacoeconomics 24(9):869-90.

Al-Ansari K, Sakran M, Davidson BL, El Sayyed R, Mahjoub H, Ibrahim K. 2010. Nebulized 5% or 3% hypertonic or 0.9% saline for treating acute bronchiolitis in infants. J Pediatr 157(4):630,4, 634.e1.

Andabaka T, Nickerson JW, Rojas-Reyes MX, Rueda JD, Bacic Vrca V, Barsic B. 2013. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. Cochrane Database Syst Rev (4):CD006602. doi(4):CD006602.

Anil AB, Anil M, Saglam AB, Cetin N, Bal A, Aksu N. 2010. High volume normal saline alone is as effective as nebulized salbutamol-normal saline, epinephrine-normal saline, and 3% saline in mild bronchiolitis. Pediatr Pulmonol 45(1):41-7.

Arora B, Mahajan P, Zidan MA, Sethuraman U. 2012. Nasopharyngeal airway pressures in bronchiolitis patients treated with high-flow nasal cannula oxygen therapy. Pediatr Emerg Care 28(11):1179-84.

Backman K, Piippo-Savolainen E, Ollikainen H, Koskela H, Korppi M. 2014. Increased asthma risk and impaired quality of life after bronchiolitis or pneumonia in infancy. Pediatr Pulmonol 49(4):318-25.

Barben J and Kuehni CE. 2014. Hypertonic saline for acute viral bronchiolitis: Take the evidence with a grain of salt. Eur Respir J 44(4):827-30.

Bont L, Steijn M, van Aalderen WM, Kimpen JL. 2004. Impact of wheezing after respiratory syncytial virus infection on health-related quality of life. Pediatr Infect Dis J 23(5):414-7.

Borckink I, Essouri S, Laurent M, Albers MJ, Burgerhof JG, Tissieres P, Kneyber MC. 2014. Infants with severe respiratory syncytial virus needed less ventilator time with nasal continuous airways pressure then invasive mechanical ventilation. Acta Paediatr 103(1):81-5.

Bressan S, Balzani M, Krauss B, Pettenazzo A, Zanconato S, Baraldi E. 2013. High-flow nasal cannula oxygen for bronchiolitis in a pediatric ward: A pilot study. Eur J Pediatr 172(12):1649-56.

Briggs A and Fenn P. 1998. Confidence intervals or surfaces? uncertainty on the cost-effectiveness plane. Health Economics 7:723-40.

Brooks CG, Harrison WN, Ralston SL. 2016. Association between hypertonic saline and hospital length of stay in acute viral bronchiolitis: A reanalysis of 2 meta-analyses. JAMA Pediatr 170(6):577-84.

Bryan MA, Desai AD, Wilson L, Wright DR, Mangione-Smith R. 2017. Association of bronchiolitis clinical pathway adherence with length of stay and costs. Pediatrics 139(3):10.1542/peds.2016,3432. Epub 2017 Feb 9.

Cangiano G, Nenna R, Frassanito A, Evangelisti M, Nicolai A, Scagnolari C, Pierangeli A, Antonelli G, Papoff P, Petrarca L, et al. 2016. Bronchiolitis: Analysis of 10 consecutive epidemic seasons. Pediatr Pulmonol .

Canty WB and Colomb-Lippa D. 2014. Using hypertonic saline to manage bronchiolitis in infants. JAAPA 27(7):45-9.

Carroll KN, Gebretsadik T, Griffin MR, Wu P, Dupont WD, Mitchel EF, Enriquez R, Hartert TV. 2008. Increasing burden and risk factors for bronchiolitis-related medical visits in infants enrolled in a state health care insurance plan. Pediatrics 122(1):58-64.

Chisholm D and Evans E. 2007. Economic evaluation in health: Saving money or improving care? Journal of Medical Economics (10):325-37.

Clarke M, Brice A, Chalmers I. 2014. Accumulating research: A systematic account of how cumulative meta-analyses would have provided knowledge, improved health, reduced harm and saved resources. PLoS One 9(7):e102670.

Cornfield DN. 2014. Bronchiolitis: Doing less and still getting better. Pediatrics 133(1):e213-4.

Crowther M, Lim W, Crowther MA. 2010. Systematic review and meta-analysis methodology. Blood 116(17):3140-6.

Cunningham S, Rodriguez A, Boyd KA, McIntosh E, Lewis SC, BIDS Collaborators Group. 2015a. Bronchiolitis of infancy discharge study (BIDS): A multicentre, parallel-group, double-blind, randomised controlled, equivalence trial with economic evaluation. Health Technol Assess 19(71):i,xxiii, 1-172.

Cunningham S, Rodriguez A, Adams T, Boyd KA, Butcher I, Enderby B, MacLean M, McCormick J, Paton JY, Wee F, et al. 2015b. Oxygen saturation targets in infants with bronchiolitis (BIDS): A double-blind, randomised, equivalence trial. Lancet 386(9998):1041-8.

De Paulis M, Gilio AE, Ferraro AA, Ferronato AE, do Sacramento PR, Botosso VF, Oliveira DB, Marinheiro JC, Harsi CM, Durigon EL, et al. 2011. Severity of viral coinfection in hospitalized infants with respiratory syncytial virus infection. J Pediatr (Rio J) 87(4):307-13.

Doucette A, Jiang X, Fryzek J, Coalson J, McLaurin K, Ambrose CS. 2016. Trends in respiratory syncytial virus and bronchiolitis hospitalization rates in high-risk infants in a united states nationally representative database, 1997-2012. PLoS One 11(4):e0152208.

Drummond M, Sculpher M, Claxton K, Stoddart G, Torrance G. 2015a. Critical assessment of economic evaluation. In: Methods for the economic évaluation of health care programmes. 4th ed. USA, New York: Oxford University Press. 41 p.

Drummond M, Sculpher M, Claxton K, Stoddart G, Torrance G. 2015b. Cost analysis. In: Methods for the economic evaluation of health care

programmes. Drummond M, Sculpher M, Claxton K, et al, editors. 4th ed. New York: Oxford University Press. 219 p.

Drysdale SB, Green CA, Sande CJ. 2016. Best practice in the prevention and management of paediatric respiratory syncytial virus infection. Ther Adv Infect Dis 3(2):63-71.

Dysart K, Miller TL, Wolfson MR, Shaffer TH. 2009. Research in high flow therapy: Mechanisms of action. Respir Med 103(10):1400-5.

Ehlken B, Ihorst G, Lippert B, Rohwedder A, Petersen G, Schumacher M, Forster J, PRIDE Study Group. 2005. Economic impact of community-acquired and nosocomial lower respiratory tract infections in young children in germany. Eur J Pediatr 164(10):607-15.

Essouri S, Laurent M, Chevret L, Durand P, Ecochard E, Gajdos V, Devictor D, Tissieres P. 2014. Improved clinical and economic outcomes in severe bronchiolitis with pre-emptive nCPAP ventilatory strategy. Intensive Care Med 40(1):84-91.

Everard ML, Hind D, Ugonna K, Freeman J, Bradburn M, Cooper CL, Cross E, Maguire C, Cantrill H, Alexander J, et al. 2014. SABRE: A multicentre randomised control trial of nebulised hypertonic saline in infants hospitalised with acute bronchiolitis. Thorax 69(12):1105-12.

Everard ML, Hind D, Ugonna K, Freeman J, Bradburn M, Dixon S, Maguire C, Cantrill H, Alexander J, Lenney W, et al. 2015. Saline in acute bronchiolitis RCT and economic evaluation: Hypertonic saline in acute bronchiolitis - randomised controlled trial and systematic review. Health Technol Assess 19(66):1-130.

Evers S, Goossens M, de Vet H, van Tulder M, Ament A. 2005. Criteria list for assessment of methodological quality of economic evaluations: Consensus on health economic criteria. Int J Technol Assess Health Care 21(2):240-5.

Farley R, Spurling GK, Eriksson L, Del Mar CB. 2014. Antibiotics for bronchiolitis in children under two years of age. Cochrane Database Syst Rev (10):CD005189. doi(10):CD005189.

Fernandes RM, Bialy LM, Vandermeer B, Tjosvold L, Plint AC, Patel H, Johnson DW, Klassen TP, Hartling L. 2013. Glucocorticoids for acute viral

bronchiolitis in infants and young children. Cochrane Database Syst Rev (6):CD004878. doi(6):CD004878.

Flores P, Mendes AL, Neto AS. 2016. A randomized trial of nebulized 3% hypertonic saline with salbutamol in the treatment of acute bronchiolitis in hospitalized infants. Pediatr Pulmonol 51(4):418-25.

Florin TA, Plint AC, Zorc JJ. 2016. Viral bronchiolitis. Lancet .

Florin TA, Shaw KN, Kittick M, Yakscoe S, Zorc JJ. 2014. Nebulized hypertonic saline for bronchiolitis in the emergency department: A randomized clinical trial. JAMA Pediatr 168(7):664-70.

Franklin D, Dalziel S, Schlapbach LJ, Babl FE, Oakley E, Craig SS, Furyk JS, Neutze J, Sinn K, Whitty JA, et al. 2015. Early high flow nasal cannula therapy in bronchiolitis, a prospective randomised control trial (protocol): A paediatric acute respiratory intervention study (PARIS). BMC Pediatr 15:183,015-0501-x.

Frey U and von Mutius E. 2009. The challenge of managing wheezing in infants. N Engl J Med 360(20):2130-3.

Fugel HJ, Nuijten M, Postma M, Redekop K. 2016. Economic evaluation in stratified medicine: Methodological issues and challenges. Front Pharmacol 7:113.

Gadomski AM and Brower M. 2010. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev (12):CD001266. doi(12):CD001266.

Garcia-Marcos L, Valverde-Molina J, Pavlovic-Nesic S, Claret-Teruel G, Penalba-Citores AC, Nehme-Alvarez D, Korta-Murua J, Sanchez-Etxaniz J, Alonso-Salas MT, Campos-Calleja C, et al. 2014. Pediatricians' attitudes and costs of bronchiolitis in the emergency department: A prospective multicentre study. Pediatr Pulmonol 49(10):1011-9.

Gil-Prieto R, Gonzalez-Escalada A, Marin-Garcia P, Gallardo-Pino C, Gil-de-Miguel A. 2015. Respiratory syncytial virus bronchiolitis in children up to 5 years of age in spain: Epidemiology and comorbidities: An observational study. Medicine (Baltimore) 94(21):e831.

Graeber SY, Zhou-Suckow Z, Schatterny J, Hirtz S, Boucher RC, Mall MA. 2013. Hypertonic saline is effective in the prevention and treatment of

mucus obstruction, but not airway inflammation, in mice with chronic obstructive lung disease. Am J Respir Cell Mol Biol 49(3):410-7.

Green CA, Yeates D, Goldacre A, Sande C, Parslow RC, McShane P, Pollard AJ, Goldacre MJ. 2016. Admission to hospital for bronchiolitis in england: Trends over five decades, geographical variation and association with perinatal characteristics and subsequent asthma. Arch Dis Child 101(2):140-6.

Grewal S, Ali S, McConnell DW, Vandermeer B, Klassen TP. 2009. A randomized trial of nebulized 3% hypertonic saline with epinephrine in the treatment of acute bronchiolitis in the emergency department. Arch Pediatr Adolesc Med 163(11):1007-12.

Grindeland CJ, Mauriello CT, Leedahl DD, Richter LM, Meyer AC. 2016. Association between updated guideline-based palivizumab administration and hospitalizations for respiratory syncytial virus infections. Pediatr Infect Dis J 35(7):728-32.

Haidich AB. 2010. Meta-analysis in medical research. Hippokratia 14(Suppl 1):29-37.

Haq I, Gopalakaje S, Fenton AC, McKean MC, J O'Brien C, Brodlie M. 2014. The evidence for high flow nasal cannula devices in infants. Paediatr Respir Rev 15(2):124-34.

Hartling L, Bialy LM, Vandermeer B, Tjosvold L, Johnson DW, Plint AC, Klassen TP, Patel H, Fernandes RM. 2011. Epinephrine for bronchiolitis. Cochrane Database Syst Rev (6):CD003123. doi(6):CD003123.

Hasegawa K, Tsugawa Y, Brown DF, Mansbach JM, Camargo CA,Jr. 2014. Temporal trends in emergency department visits for bronchiolitis in the united states, 2006 to 2010. Pediatr Infect Dis J 33(1):11-8.

Hasegawa K, Tsugawa Y, Brown DF, Mansbach JM, Camargo CA,Jr. 2013a. Trends in bronchiolitis hospitalizations in the united states, 2000-2009. Pediatrics 132(1):28-36.

Hasegawa K, Tsugawa Y, Brown DF, Mansbach JM, Camargo CA,Jr. 2013b. Trends in bronchiolitis hospitalizations in the united states, 2000-2009. Pediatrics 132(1):28-36.

Hasegawa K, Pate BM, Mansbach JM, Macias CG, Fisher ES, Piedra PA, Espinola JA, Sullivan AF, Camargo CA,Jr. 2015. Risk factors for requiring intensive care among children admitted to ward with bronchiolitis. Acad Pediatr 15(1):77-81.

Heikkila P and Korppi M. 2016. Nebulised hypertonic saline inhalations do not shorten hospital stays in infants with bronchiolitis. Acta Paediatr 105(9):1036-8.

Hervas D, Reina J, Yanez A, del Valle JM, Figuerola J, Hervas JA. 2012. Epidemiology of hospitalization for acute bronchiolitis in children: Differences between RSV and non-RSV bronchiolitis. Eur J Clin Microbiol Infect Dis 31(8):1975-81.

Higgins J and Green S, editors. 2011. Cochrane handbook for systematic reviews of interventions version 5.1.0. http://handbook.cochrane.org.: The Cochrane Collaboration.

Higgins JP, Thompson SG, Deeks JJ, Altman DG. 2003. Measuring inconsistency in meta-analyses. BMJ 327(7414):557-60.

Hilliard TN, Archer N, Laura H, Heraghty J, Cottis H, Mills K, Ball S, Davis P. 2012. Pilot study of vapotherm oxygen delivery in moderately severe bronchiolitis. Arch Dis Child 97(2):182-3.

Hogan AB, Anderssen RS, Davis S, Moore HC, Lim FJ, Fathima P, Glass K. 2016. Time series analysis of RSV and bronchiolitis seasonality in temperate and tropical western australia. Epidemics 16:49-55.

Hough JL, Pham TM, Schibler A. 2014. Physiologic effect of high-flow nasal cannula in infants with bronchiolitis. Pediatr Crit Care Med 15(5):e214-9.

Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F, Briggs AH, Mauskopf J, Loder E, et al. 2013. Consolidated health economic evaluation reporting standards (CHEERS) statement. Value Health 16(2):e1-5.

Hutchings FA, Hilliard TN, Davis PJ. 2015. Heated humidified high-flow nasal cannula therapy in children. Arch Dis Child 100(6):571-5.

Iacobelli S, Combier E, Roussot A, Cottenet J, Gouyon JB, Quantin C. 2017. Gestational age and 1-year hospital admission or mortality: A nation-wide population-based study. BMC Pediatr 17(1):28,017-0787-y.

Ipek IO, Yalcin EU, Sezer RG, Bozaykut A. 2011. The efficacy of nebulized salbutamol, hypertonic saline and salbutamol/hypertonic saline combination in moderate bronchiolitis. Pulm Pharmacol Ther 24(6):633-7.

Jacobs JD, Foster M, Wan J, Pershad J. 2014. 7% hypertonic saline in acute bronchiolitis: A randomized controlled trial. Pediatrics 133(1):e8-13.

Jamison D, Breman J, Measham A, et al. e. 2006. Chapter 3, cost-effectiveness analysis. In: Priorities in health. Washington (DC): The International Bank for Reconstruction and Development / The World Bank.

Jartti T, Aakula M, Mansbach JM, Piedra PA, Bergroth E, Koponen P, Kivisto JE, Sullivan AF, Espinola JA, Remes S, et al. 2014. Hospital length-of-stay is associated with rhinovirus etiology of bronchiolitis. Pediatr Infect Dis J 33(8):829-34.

Jat KR and Mathew JL. 2015. Continuous positive airway pressure (CPAP) for acute bronchiolitis in children. Cochrane Database Syst Rev 1:CD010473.

Kallappa C, Hufton M, Millen G, Ninan TK. 2014. Use of high flow nasal cannula oxygen (HFNCO) in infants with bronchiolitis on a paediatric ward: A 3-year experience. Arch Dis Child 99(8):790-1.

Kelly GS, Simon HK, Sturm JJ. 2013. High-flow nasal cannula use in children with respiratory distress in the emergency department: Predicting the need for subsequent intubation. Pediatr Emerg Care 29(8):888-92.

Kepreotes E, Whitehead B, Attia J, Oldmeadow C, Collison A, Searles A, Goddard B, Hilton J, Lee M, Mattes J. 2017. High-flow warm humidified oxygen versus standard low-flow nasal cannula oxygen for moderate bronchiolitis (HFWHO RCT): An open, phase 4, randomised controlled trial. Lancet 389(10072):930-9.

Khanal A, Sharma A, Basnet S, Sharma PR, Gami FC. 2015. Nebulised hypertonic saline (3%) among children with mild to moderately severe bronchiolitis--a double blind randomized controlled trial. BMC Pediatr 15:115,015-0434-4.

Klein DJ, Brown AD, Detsky AS. 2016. Investing wisely in health care capital. JAMA 316(15):1543-4.

Korppi M. 2015. Bronchiolitis: The disease of <6-month-old, <12-month-old or <24-month-old infants. Pediatr Infect Dis J 34(7):799-800.

Korppi M, Koponen P, Nuolivirta K. 2012. Upper age limit for bronchiolitis: 12 months or 6 months? Eur Respir J 39(3):787,8; author reply 788-9.

Kose S, Sehriyaroglu A, Esen F, Ozdemir A, Kardas Z, Altug U, Karakus E, Ozcan A, Kisaarslan AF, Elmali F, et al. 2016. Comparing the efficacy of 7%, 3% and 0.9% saline in moderate to severe bronchiolitis in infants. Balkan Med J 33(2):193-7.

Kotecha SJ, Adappa R, Gupta N, Watkins WJ, Kotecha S, Chakraborty M. 2015. Safety and efficacy of high-flow nasal cannula therapy in preterm infants: A meta-analysis. Pediatrics 136(3):542-53.

Kuzik BA, Al-Qadhi SA, Kent S, Flavin MP, Hopman W, Hotte S, Gander S. 2007. Nebulized hypertonic saline in the treatment of viral bronchiolitis in infants. J Pediatr 151(3):266,70, 270.e1.

Lambert SB, Allen KM, Carter RC, Nolan TM. 2008. The cost of community-managed viral respiratory illnesses in a cohort of healthy preschool-aged children. Respir Res 9:11,9921-9-11.

Lanari M, Prinelli F, Adorni F, Di Santo S, Vandini S, Silvestri M, Musicco M, Study Group of Italian Society of Neonatology on Risk Factors for RSV Hospitalization. 2015. Risk factors for bronchiolitis hospitalization during the first year of life in a multicenter italian birth cohort. Ital J Pediatr 41:40,015-0149-z.

Leader S and Kohlhase K. 2003. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. J Pediatr 143(5 Suppl):S127-32.

Luo Z, Liu E, Luo J, Li S, Zeng F, Yang X, Fu Z. 2010. Nebulized hypertonic saline/salbutamol solution treatment in hospitalized children with mild to moderate bronchiolitis. Pediatr Int 52(2):199-202.

Luo Z, Fu Z, Liu E, Xu X, Fu X, Peng D, Liu Y, Li S, Zeng F, Yang X. 2011. Nebulized hypertonic saline treatment in hospitalized children with

moderate to severe viral bronchiolitis. Clin Microbiol Infect 17(12):1829-33.

Maguire C, Cantrill H, Hind D, Bradburn M, Everard ML. 2015. Hypertonic saline (HS) for acute bronchiolitis: Systematic review and meta-analysis. BMC Pulm Med 15:148,015-0140-x.

Mahesh Kumar K, Karunakara B, Manjunath M, Mallikarjuna H. 2013. Aerosolised hypertonic saline in hospitalized youg children with acute bronchiolitis: A randomized controlled clinical trial. Journal of Pediatric Sciences 5(1):e174.

Mandelberg A and Amirav I. 2010a. Hypertonic saline or high volume normal saline for viral bronchiolitis: Mechanisms and rationale. Pediatr Pulmonol 45(1):36-40.

Mandelberg A and Amirav I. 2010b. Hypertonic saline in the treatment of acute bronchiolitis in the emergency department. Arch Pediatr Adolesc Med 164(4):395,6; author reply 396-7.

Mandelberg A, Tal G, Witzling M, Someck E, Houri S, Balin A, Priel IE. 2003. Nebulized 3% hypertonic saline solution treatment in hospitalized infants with viral bronchiolitis. Chest 123(2):481-7.

Mansbach JM, Piedra PA, Stevenson MD, Sullivan AF, Forgey TF, Clark S, Espinola JA, Camargo CA,Jr, MARC-30 Investigators. 2012. Prospective multicenter study of children with bronchiolitis requiring mechanical ventilation. Pediatrics 130(3):e492-500.

Matveinen P and Knape N. 2016. Health expenditure and financing 2014. National institute for health and welfare. Report nr 13/2016.

Mayfield S, Bogossian F, O'Malley L, Schibler A. 2014. High-flow nasal cannula oxygen therapy for infants with bronchiolitis: Pilot study. J Paediatr Child Health 50(5):373-8.

McKiernan C, Chua LC, Visintainer PF, Allen H. 2010. High flow nasal cannulae therapy in infants with bronchiolitis. J Pediatr 156(4):634-8.

Mecklin M, Hesselmar B, Qvist E, Wennergren G, Korppi M. 2014. Diagnosis and treatment of bronchiolitis in finnish and swedish children's hospitals. Acta Paediatr 103(9):946-50.

Meissner HC. 2016. Viral bronchiolitis in children. N Engl J Med 374(18):1793-4.

Meltzer MI. 2001. Introduction to health economics for physicians. Lancet 358(9286):993-8.

Metge P, Grimaldi C, Hassid S, Thomachot L, Loundou A, Martin C, Michel F. 2014. Comparison of a high-flow humidified nasal cannula to nasal continuous positive airway pressure in children with acute bronchiolitis: Experience in a pediatric intensive care unit. Eur J Pediatr 173(7):953-8.

Miedema CJ, Kors AW, Tjon A Ten WE, Kimpen JL. 2001. Medical consumption and socioeconomic effects of infection with respiratory syncytial virus in the netherlands. Pediatr Infect Dis J 20(2):160-3.

Mikalsen IB, Davis P, Oymar K. 2016. High flow nasal cannula in children: A literature review. Scand J Trauma Resusc Emerg Med 24:93,016-0278-4.

Milani GP, Plebani AM, Arturi E, Brusa D, Esposito S, Dell'Era L, Laicini EA, Consonni D, Agostoni C, Fossali EF. 2016. Using a high-flow nasal cannula provided superior results to low-flow oxygen delivery in moderate to severe bronchiolitis. Acta Paediatr .

Milesi C, Boubal M, Jacquot A, Baleine J, Durand S, Odena MP, Cambonie G. 2014. High-flow nasal cannula: Recommendations for daily practice in pediatrics. Ann Intensive Care 4:29,014-0029-5. eCollection 2014.

Milesi C, Baleine J, Matecki S, Durand S, Combes C, Novais AR, Cambonie G. 2013. Is treatment with a high flow nasal cannula effective in acute viral bronchiolitis? A physiologic study. Intensive Care Med 39(6):1088-94.

Miller EK, Gebretsadik T, Carroll KN, Dupont WD, Mohamed YA, Morin LL, Heil L, Minton PA, Woodward K, Liu Z, et al. 2013. Viral etiologies of infant bronchiolitis, croup and upper respiratory illness during 4 consecutive years. Pediatr Infect Dis J 32(9):950-5.

Miraglia Del Giudice M, Saitta F, Leonardi S, Capasso M, Niglio B, Chinellato I, Decimo F, Maiello N, Capristo C, Perrone L, et al. 2012. Effectiveness of nebulized hypertonic saline and epinephrine in hospitalized infants with bronchiolitis. Int J Immunopathol Pharmacol 25(2):485-91.

Mongan JJ, Ferris TG, Lee TH. 2008. Options for slowing the growth of health care costs. N Engl J Med 358(14):1509-14.

Morris S, Devlin N, Parkin D. 2009a. Introduction to economic analysis in health care. In: Economic analysis in health care. Great Britain, Glasgow: John Wiley & Sons, Ltd. 1 p.

Morris S, Devlin N, Parkin D. 2009b. The production and costs of health care. In: Economic analysis in health care. West Sussex, England: John Wiley & Sons, Ltd. 59 p.

Morris S, Devlin N, Parkin D. 2009c. Economic evaluation methods. In: Economic analysis in health care. West Sussex, England: John Wiley & Sons, Ltd. 305 p.

Mullins CD, Onwudiwe NC, Branco de Araújo GT, Chen W, Xuan J, Tichopád A, Hu S. 2014. Guidance document: Global pharmacoeconomic model adaption strategies. Value in Health Regional Issues 5:7-13.

Murray J, Bottle A, Sharland M, Modi N, Aylin P, Majeed A, Saxena S, Medicines for Neonates Investigator Group. 2014. Risk factors for hospital admission with RSV bronchiolitis in england: A population-based birth cohort study. PLoS One 9(2):e89186.

Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, O'Brien KL, Roca A, Wright PF, Bruce N, et al. 2010. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: A systematic review and meta-analysis. Lancet 375(9725):1545-55.

National Collaborating Centre for Women's and Children's Health (UK). 2015. .

Statistic [Internet]; c2016 [cited 2016 10/24]. Available from: https://sampo.thl.fi/pivot/prod/fi/ttr/shp/fact_shp?row=area-12260&column=time-12059&filter=reportgroup-12132&filter=area-12260&filter=agegroup-12299&filter=measure-73006 .

New Born 2012 - Statistical Report [Internet] [cited 2012 . Available from: http://www.julkari.fi/bitstream/handle/10024/110752/Tr32_13.pdf?sequence=4 .

Nenna R, Papoff P, Moretti C, De Angelis D, Battaglia M, Papasso S, Bernabucci M, Cangiano G, Petrarca L, Salvadei S, et al. 2014. Seven

percent hypertonic saline--0.1% hyaluronic acid in infants with mild-to-moderate bronchiolitis. Pediatr Pulmonol 49(9):919-25.

Neumann PJ and Sanders GD. 2017. Cost-effectiveness analysis 2.0. N Engl J Med 376(3):203-5.

Neumann PJ, Rosen AB, Weinstein MC. 2005. Medicare and cost-effectiveness analysis. N Engl J Med 353(14):1516-22.

Nordmann AJ, Kasenda B, Briel M. 2012. Meta-analyses: What they can and cannot do. Swiss Med Wkly 142:w13518.

Oakley E, Bata S, Rengasamy S, Krieser D, Cheek J, Jachno K, Babl FE. 2016. Nasogastric hydration in infants with bronchiolitis less than 2 months of age. J Pediatr .

Health expenditure and financing [Internet]; c2016 [cited 2017 5/20]. Available from: http://stats.oecd.org/Index.aspx?DataSetCode=SHA .

Ojha AR, Mathema S, Sah S, Aryal UR. 2014. A comparative study on use of 3% saline versus 0.9% saline nebulization in children with bronchiolitis. J Nepal Health Res Counc 12(26):39-43.

Hypertonic Saline for Bronchiolitis. openMetaAnalysis. [Internet]; c2016 [cited 2016 11.02]. Available from: http://openmetaanalysis.github.io/Hypertonic-Saline-for-Bronchiolitis/. .

Overmann KM and Florin TA. 2016. Nebulised hypertonic saline may be less effective than previously reported in reducing hospital length of stay and admission rate in acute bronchiolitis. Evid Based Med 21(4):143,2016-110452. Epub 2016 May 24.

Oymar K and Bardsen K. 2014. Continuous positive airway pressure for bronchiolitis in a general paediatric ward; a feasibility study. BMC Pediatr 14:122,2431-14-122.

Oymar K, Skjerven HO, Mikalsen IB. 2014. Acute bronchiolitis in infants, a review. Scand J Trauma Resusc Emerg Med 22:23,7241-22-23.

Palmer L, Hall CB, Katkin JP, Shi N, Masaquel AS, McLaurin KK, Mahadevia PJ. 2011. Respiratory outcomes, utilization and costs 12 months following

a respiratory syncytial virus diagnosis among commercially insured late-preterm infants. Curr Med Res Opin 27(2):403-12.

Pandit S, Dhawan N, Thakur D. 2013. <br />Utility of hypertonic saline in the management of acute bronchiolitis in infants: A randomised controlled study International Journal of Clinical Pediatrics 2(1):24-9.

Panozzo CA, Fowlkes AL, Anderson LJ. 2007. Variation in timing of respiratory syncytial virus outbreaks: Lessons from national surveillance. Pediatr Infect Dis J 26(11 Suppl):S41-5.

Pelletier AJ, Mansbach JM, Camargo CA,Jr. 2006. Direct medical costs of bronchiolitis hospitalizations in the united states. Pediatrics 118(6):2418-23.

Perez-Yarza EG, Moreno-Galdo A, Ramilo O, Rubi T, Escribano A, Torres A, Sardon O, Oliva C, Perez G, Cortell I, et al. 2015. Risk factors for bronchiolitis, recurrent wheezing, and related hospitalization in preterm infants during the first year of life. Pediatr Allergy Immunol 26(8):797-804.

Pham TM, O'Malley L, Mayfield S, Martin S, Schibler A. 2015. The effect of high flow nasal cannula therapy on the work of breathing in infants with bronchiolitis. Pediatr Pulmonol 50(7):713-20.

Pogue JM and Yusuf S. 1997. Cumulating evidence from randomized trials: Utilizing sequential monitoring boundaries for cumulative meta-analysis. Control Clin Trials 18(6):580,93; discussion 661-6.

Pruikkonen H, Uhari M, Dunder T, Pokka T, Renko M. 2014. Infants under 6 months with bronchiolitis are most likely to need major medical interventions in the 5 days after onset. Acta Paediatr 103(10):1089-93.

Ralston SL, Lieberthal AS, Meissner HC, Alverson BK, Baley JE, Gadomski AM, Johnson DW, Light MJ, Maraqa NF, Mendonca EA, et al. 2014. Clinical practice guideline: The diagnosis, management, and prevention of bronchiolitis. Pediatrics 134(5):e1474-502.

Rawlins MD. 2016. Cost, effectiveness, and value: How to judge? JAMA 316(14):1447-8.

Ricci V, Delgado Nunes V, Murphy MS, Cunningham S, Guideline Development Group and Technical Team. 2015. Bronchiolitis in children: Summary of NICE guidance. BMJ 350:h2305.

Riese J, Fierce J, Riese A, Alverson BK. 2015. Effect of a hospital-wide high-flow nasal cannula protocol on clinical outcomes and resource utilization of bronchiolitis patients admitted to the PICU. Hosp Pediatr 5(12):613-8.

Roggeri DP, Roggeri A, Rossi E, Cataudella S, Martini N. 2016. Impact of hospitalizations for bronchiolitis in preterm infants on long-term health care costs in italy: A retrospective case-control study. Clinicoecon Outcomes Res 8:407-12.

Rolfsjord LB, Skjerven HO, Carlsen KH, Mowinckel P, Bains KE, Bakkeheim E, Lodrup Carlsen KC. 2016. The severity of acute bronchiolitis in infants was associated with quality of life nine months later. Acta Paediatr 105(7):834-41.

Rolfsjord LB, Skjerven HO, Bakkeheim E, Carlsen KH, Hunderi JO, Kvenshagen BK, Mowinckel P, Lodrup Carlsen KC. 2015. Children hospitalised with bronchiolitis in the first year of life have a lower quality of life nine months later. Acta Paediatr 104(1):53-8.

Roque i Figuls M, Gine-Garriga M, Granados Rugeles C, Perrotta C, Vilaro J. 2016. Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old. Cochrane Database Syst Rev 2:CD004873.

Rudmik L and Drummond M. 2013. Health economic evaluation: Important principles and methodology. Laryngoscope 123(6):1341-7.

Ryder HF, McDonough C, Tosteson AN, Lurie JD. 2009. Decision analysis and cost-effectiveness analysis. Semin Spine Surg 21(4):216-22.

Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, Kuntz KM, Meltzer DO, Owens DK, Prosser LA, et al. 2016. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second panel on cost-effectiveness in health and medicine. JAMA 316(10):1093-103.

Schibler A, Pham TM, Dunster KR, Foster K, Barlow A, Gibbons K, Hough JL. 2011. Reduced intubation rates for infants after introduction of high-flow nasal prong oxygen delivery. Intensive Care Med 37(5):847-52.

Schuh S, Freedman S, Coates A, Allen U, Parkin PC, Stephens D, Ungar W, DaSilva Z, Willan AR. 2014. Effect of oximetry on hospitalization in bronchiolitis: A randomized clinical trial. JAMA 312(7):712-8.

Sedgwick P. 2013. Meta-analyses: How to read a funnel plot. BMJ (Clinical Research Ed.) 346:f1342.

Sharma BS, Gupta MK, Rafik SP. 2013. Hypertonic (3%) saline vs 0.93% saline nebulization for acute viral bronchiolitis: A randomized controlled trial. Indian Pediatr 50(8):743-7.

Shi N, Palmer L, Chu BC, Katkin JP, Hall CB, Masaquel AS, Mahadevia PJ. 2011. Association of RSV lower respiratory tract infection and subsequent healthcare use and costs: A medicaid claims analysis in early-preterm, late-preterm, and full-term infants. J Med Econ 14(3):335-40.

Sinha IP, McBride AK, Smith R, Fernandes RM. 2015. CPAP and high-flow nasal cannula oxygen in bronchiolitis. Chest 148(3):810-23.

Skjerven HO, Megremis S, Papadopoulos NG, Mowinckel P, Carlsen KH, Lodrup Carlsen KC, ORAACLE Study Group. 2016. Virus type and genomic load in acute bronchiolitis: Severity and treatment response with inhaled adrenaline. J Infect Dis 213(6):915-21.

Skjerven HO, Rolfsjord LB, Berents TL, Engen H, Dizdarevic E, Midgaard C, Kvenshagen B, Aas MH, Hunderi JO, Bains KE, et al. 2015. Allergic diseases and the effect of inhaled epinephrine in children with acute bronchiolitis: Follow-up from the randomised, controlled, double-blind, bronchiolitis ALL trial. Lancet Respir Med 3(9):702-8.

Skjerven HO, Hunderi JO, Brugmann-Pieper SK, Brun AC, Engen H, Eskedal L, Haavaldsen M, Kvenshagen B, Lunde J, Rolfsjord LB, et al. 2013. Racemic adrenaline and inhalation strategies in acute bronchiolitis. N Engl J Med 368(24):2286-93.

Smyth RL and Openshaw PJ. 2006. Bronchiolitis. Lancet 368(9532):312-22.

Spuijbroek AT, Oostenbrink R, Landgraf JM, Rietveld E, de Goede-Bolder A, van Beeck EF, van Baar M, Raat H, Moll HA. 2011. Health-related quality of life in preschool children in five health conditions. Qual Life Res 20(5):779-86.

Stahl JE. 2008. Modelling methods for pharmacoeconomics and health technology assessment: An overview and guide. Pharmacoeconomics 26(2):131-48.

Population [Internet]; c2016 [cited 2017 4/4]. Available from: http://tilastokeskus.fi/tup/suoluk/suoluk_vaesto.html .

Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, Carpenter J, Rucker G, Harbord RM, Schmid CH, et al. 2011. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 343:d4002.

Stinnett A and Mullahy J. 1997. The negative side of cost-effectiveness analysis. Journal of the American Medical Association 277(24):1931-2.

Tal G, Cesar K, Oron A, Houri S, Ballin A, Mandelberg A. 2006. Hypertonic saline/epinephrine treatment in hospitalized infants with viral bronchiolitis reduces hospitalization stay: 2 years experience. Isr Med Assoc J 8(3):169-73.

Tapiainen T, Aittoniemi J, Immonen J, Jylkka H, Meinander T, Nuolivirta K, Peltola V, Salo E, Seuri R, Walle SM, et al. 2016. Finnish guidelines for the treatment of laryngitis, wheezing bronchitis and bronchiolitis in children. Acta Paediatr 105(1):44-9.

Taylor S, Taylor RJ, Lustig RL, Schuck-Paim C, Haguinet F, Webb DJ, Logie J, Matias G, Fleming DM. 2016. Modelling estimates of the burden of respiratory syncytial virus infection in children in the UK. BMJ Open 6(6).

Teunissen J, Hochs AH, Vaessen-Verberne A, Boehmer AL, Smeets CC, Brackel H, van Gent R, Wesseling J, Logtens-Stevens D, de Moor R, et al. 2014. The effect of 3% and 6% hypertonic saline in viral bronchiolitis: A randomised controlled trial. Eur Respir J 44(4):913-21.

Tinsa F, Abdelkafi S, Bel Haj I, Hamouda S, Brini I, Zouari B, Boussetta K. 2014. A randomized, controlled trial of nebulized 5% hypertonic saline and mixed 5% hypertonic saline with epinephrine in bronchiolitis. Tunis Med 92(11):674-7.

Wang D, Bayliss S, Meads C. 2011. Palivizumab for immunoprophylaxis of respiratory syncytial virus (RSV) bronchiolitis in high-risk infants and

young children: A systematic review and additional economic modelling of subgroup analyses. Health Technol Assess 15(5):iii,iv, 1-124.

Werner E, Wheeler S, Burd I. 2012. Creating decision trees to assess cost-effectiveness in clinical research. J Biomet Biostat :S7-4.

Wu S, Baker C, Lang ME, Schrager SM, Liley FF, Papa C, Mira V, Balkian A, Mason WH. 2014. Nebulized hypertonic saline for bronchiolitis: A randomized clinical trial. JAMA Pediatr 168(7):657-63.

Yong JH, Schuh S, Rashidi R, Vanderby S, Lau R, Laporte A, Nauenberg E, Ungar WJ. 2009. A cost effectiveness analysis of omitting radiography in diagnosis of acute bronchiolitis. Pediatr Pulmonol 44(2):122-7.

Zervou FN, Zacharioudakis IM, Pliakos EE, Grigoras CA, Ziakas PD, Mylonakis E. 2015. Adaptation of cost analysis studies in practice guidelines. Medicine (Baltimore) 94(52):e2365.

Zhang L, Mendoza-Sassi RA, Klassen TP, Wainwright C. 2015. Nebulized hypertonic saline for acute bronchiolitis: A systematic review. Pediatrics 136(4):687-701.

Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP. 2013. Nebulised hypertonic saline solution for acute bronchiolitis in infants. Cochrane Database Syst Rev (7):CD006458. doi(7):CD006458.

Zorc JJ and Hall CB. 2010. Bronchiolitis: Recent evidence on diagnosis and management. Pediatrics 125(2):342-9.

# APPENDIX

**Table 7.** Appendix table. The details of the studies including in the cumulative meta-analysis, presented first inpatient and second outpatient settings (Original IV).

| Study | Intervention and comparison | Population | Result mean ± SD |
|---|---|---|---|
| Al-Ansari et al, 2010, Qatar | 5% and 3% hypertonic saline compared to 0.9% saline inhalations every four hours, all HS and NS inhalations 5mL with epinephrine | Infants under 18 months of age<br><br>5% HS, n=57, mean age 4.02 ± 2.56<br><br>3% HS, n=58, mean age 3.84 ± 2.84<br><br>0.9% NS, n=56, mean age 3.30 ± 2.43 | LOS:<br><br>5% HS, 1.56 ± 1.38 days<br><br>3% HS, 1.4 ± 1.41 days<br><br>0.9% NS, 1.88 ± 1.76 days |
| Everard et al, 2014, UK | 3% HS 4mL inhalations every six hours compared to supportive care without inhalations | Infants under 12 months of age<br><br>3% HS, n=141, mean age 2.3<br><br>supportive care, n=149, mean age 2.5 | LOS:<br><br>3% HS, 3.3 ± 2.6 days<br><br>supportive care, 3.4 ± 2.8 days |

| Flores et al, 2016, Portugal | 3% HS compared to 0.9% NS inhalations, both HS and NS 3mL with salbutamol every six hours | Infants under 12 months of age<br><br>3% HS, n=33, mean age 3.3 ± 2.4<br><br>0.9% NS, n=35, mean age 3.8 ± 2.5 | LOS:<br><br>3% HS, 5.6 ± 2.3 days<br><br>0.9% NS, 5.4 ± 2.1 days |
|---|---|---|---|
| Kuzik et al, 2007, United Arab Emirates and Canada | 3% HS compared to 0.9% NS inhalations every four hours at first five doses and then every six hours, both HS and NS 4mL | Infants under 18 months of age<br><br>3% HS, n=47, mean age 4.4 ± 3.7<br><br>0.9% NS, n=49, mean age 4.6 ± 4.7 | LOS:<br><br>3% HS, 2.6 ± 1.9 days<br><br>0.9% NS, 3.5 ± 2.9 days |
| Köse et al, 2016, Turkey | 7% and 3% HS compared to 0.9% NS inhalations every six hours, all HS and NS inhalations 2.5mL with salbutamol | Infants 1 ≤ 24 months of age<br><br>7% HS, n=34, median age 7.7<br><br>3% HS, n=35, median age 7.6<br><br>0.9% NS, n=35, median age 7.6 | LOS:<br><br>7% HS, 3.4 ± 2.4 days<br><br>3% HS, 2.8 ± 1.8 days<br><br>0.9% NS, 3.2 ± 2.4 days |
| Luo et al, 2010, China | 3% HS compared to 0.9% NS inhalations every eight hours, both HS and NS 4mL with salbutamol | Infants under 24 months of age<br><br>3% HS, n=50, mean age 6.0 ± 4.3<br><br>0.9% NS, n=43, mean age 5.6 ± 4.5 | LOS:<br><br>3% HS, 6.0 ± 1.2 days<br><br>0.9% NS, 7.4 ± 1.5 days |

| | | | |
|---|---|---|---|
| Luo et al, 2011, China | 3% HS compared to 0.9% NS inhalations every two hours for first three doses, then every four hours for five doses and then every six hours, both HS and NS 4mL | Infants under 24 months of age<br><br>3% HS, n=57, mean age 5.9 ± 4.1<br><br>0.9% NS, n=55, mean age 5.8 ± 4.3 | LOS:<br><br>3% HS, 4.8 ± 1.2 days<br><br>0.9% NS, 6.4 ± 1.4 days |
| Mahesh Kumar et al, 2013, India | 3% HS compared to 0.9% NS inhalations every six hours, both HS and NS 3mL with salbutamol | Infants under 24 months of age<br><br>3% HS, n=20<br><br>0.9% NS, n=20<br><br>mean age 5.93 ± 3.83 months | LOS:<br><br>3% HS, 2.25 ± 0.89 days<br><br>0.9% NS, 2.88 ± 1.76 days |
| Mandelberg et al, 2003, Israel | 3% HS compared to 0.9% NS inhalations every eight hours, both HS and NS 4mL with epinephrine | Infants under 12 months of age<br><br>3% HS, n=27, mean age 3 ± 1.2<br><br>0.9% NS, n=25, mean age 2.6 ± 1.9 | LOS:<br><br>3% HS, 3 ± 1.2 days<br><br>0.9% NS, 4 ± 1.9 days |
| Miraglia et al, 2012, Italy | 3% HS with epinephrine compared to 0.9% NS inhalations every six hours, doses as mL not reported | Infants under 12 months of age<br><br>3% HS, n=52, mean age 4.8 ± 2.3<br><br>0.9% NS, n=54, mean age 4.2 ± 1.6 | LOS:<br><br>3% HS, 4.9 ± 1.3 days<br><br>0.9% NS, 5.6 ± 1.6 days |

| Nenna et al, 2014, Italy | 7% HS with hyaluronic acid compared to 0.9% NS inhalations twice a day, both HS and NS 2.5mL | Infants under 12 months of age<br><br>7% HS, n=21, median age 2 (0.5-7)<br><br>0.9% NS, n=18, median age 2 (0.5-6) | LOS:<br><br>7% HS, 4.1 ± 1.2 days<br><br>0.9% NS, 4.8 ± 1.5 days |
|---|---|---|---|
| Ojha et al, 2014, Nepal | 3% HS compared to 0.9% NS inhalations every eight hours, both HS and NS 4mL | Infants between six weeks and 24 months of age<br><br>3% HS, n=31, mean age 8.61 ± 5.7<br><br>0.9% NS, n=26, mean age 8.51 ± 4.2 | LOS:<br><br>3% HS, 1.87 ± 0.96 days<br><br>0.9% NS, 1.82 ± 1.18 days |
| Pandit et al, 2013, India | 3% HS compared to 0.9% NS inhalations first three doses every hour and thereafter every six hours, both HS and NS 4mL with adrenaline | Infants 2 ≤ 12 months of age<br><br>3% HS, n=51<br><br>0.9% NS, n=49<br><br>mean age not reported | LOS:<br><br>3% HS, 3.92 ± 1.72 days<br><br>0.9% NS, 4.08 ± 1.90 days |
| Sharma et al, 2013, India | 3% HS compared to 0.9% NS inhalations every four hours, both HS and NS 4mL with salbutamol | Infants 1 ≤ 24 months of age<br><br>3% HS, n=125, mean age 4.93 ± 4.31<br><br>0.9% NS, n=123, mean age 4.18 ± 4.24 | LOS:<br><br>3% HS, 2.65 ± 0.98 days<br><br>0.9% NS, 2.66 ± 0.93 days |

| Tal et al, 2006, Israel | 3% HS compared to 0.9% NS inhalations every eight hours, both HS and NS 4mL with epinephrine | Infants under 12 months of age<br><br>3% HS, n=21, mean age 2.8 ± 1.2<br><br>0.9% NS, n=20, mean age 2.3 ± 0.7 | LOS:<br><br>3% HS, 2.6 ± 1.4 days<br><br>0.9% NS, 3.5 ± 1.7 days |
|---|---|---|---|
| Teunissen et al, 2014, Netherlands | 6% and 3% HS compared to 0.9% NS inhalations every eight hours, all HS and NS inhalations 4mL with salbutamol | Infants under 24 months of age<br><br>6% HS, n=83, mean age 3.4 (IQR 3.8)<br><br>3% HS, n=84, mean age 3.6 (IQR 5.2)<br><br>HS altogether n=167<br><br>0.9% NS, n=80, mean age 3.6 (IQR 5.0) | LOS:<br><br>3% and 6% HS, 3.03 ± 1.95 days<br><br>0.9% NS, 2.47 ± 1.6 days |
| Tinsa et al, 2014, Tunis | 5% HS with or without epinephrine compare to 0.9% NS inhalations every four hours, all HS and NS inhalations 4mL | Infants 1 ≤ 12 months of age<br><br>5% HS, n=31, mean age 3.76 ± 2.8<br><br>5% HS+e, n=36, mean age 3.28 ± 2.53<br><br>0.9% NS, n=26, mean age 3.06 ± 2.47 | LOS:<br><br>5% HS, 3.6 ± 1.7 days<br><br>5% HS+e, 3.5 ± 1.97 days<br><br>0.9% NS, 4.48 ± 3.81 days |
| Wu et al, 2014, USA | 3% HS compared to 0.9% NS inhalations every eight hours, both HS and NS 4mL | Infants under 24 months of age<br><br>3% HS, n=61<br><br>0.9% NS, n=84 | LOS:<br><br>3% HS, 3.16 ± 2.11 days<br><br>0.9% NS, 3.92 ± 5.24 days |

| Study | Intervention and comparison | Population | Result events/total number |
|---|---|---|---|
| Angoulvant et al, 2017 France | 3% HS compared to 0.9% NS inhalations twice in the ED | Infants between six weeks and 12 months of age<br><br>3% HS, n=385, median age 3 (2-5)<br><br>0.9% NS, n= 390, median age 3 (2-5) | Admission rate:<br><br>3% HS, 185/385 (48.1%)<br><br>0.9% NS, 202/387 (52.5%) |
| Anil et al, 2009 Turkey | 3% HS compared to 0.9 NS inhalations, all HS and NS inhalations 4mL, with either epinephrine or salbutamol or NS alone (five groups) | Infants under 24 months of age<br><br>3% HS, n=75<br><br>0.9% NS, n=111<br><br>mean age $9.5 \pm 5.3$ | Admission rate:<br><br>3% HS, 1/75 (1.3%)<br><br>0.9% NS, 1/111 (0.9%) |
| Florin et al, 2014, USA | 3% HS compared to 0.9% NS inhalations, both HS and NS 4mL and within 90 minutes after albuterol | Infants $2 \leq 24$ months of age<br><br>3% HS, n=31, mean age $7.2 \pm 5.1$<br><br>0.9% NS, n=31, mean age $6.1 \pm 3.6$ | Admission rate:<br><br>3% HS, 22/31 (71%)<br><br>0.9% NS, 20/31 (64.5%) |
| Grewal et al, 2009, Canada | 3% HS compared to 0.9% NS inhalations, both HS and NS 2.5mL with racemic epinephrine | Infants between six weeks and 12 months of age<br><br>3% HS, n=23, mean age $5.6 \pm 4.0$<br><br>0.9% NS, n=23, mean age $4.4 \pm 3.4$ | Admission rate:<br><br>3% HS, 8/23 (34.8%)<br><br>0.9% NS, 13/23 (56.5%) |

| Ipek et al, 2011, Turkey | 3% HS compared to 0.9% NS inhalations every 20 min until three doses, both HS and NS 4mL, with or without salbutamol (four groups) | Infants under 24 months of age<br><br>3% HS, n=60<br><br>0.9% NS, n=60<br><br>mean age 7.96 ± 3.91 | Admission rate:<br><br>3% HS, 5/60 (8.3%)<br><br>0.9% NS, 8/60 (13.3%) |
|---|---|---|---|
| Jacobs et al, 2014, USA | 7% HS compared to 0.9% NS inhalations once, both HS and NS 3mL with racemic epinephrine | Infants between six weeks and 24 months of age<br><br>7% HS, n=52, mean age 6.0 ± 3.9<br><br>0.9% NS, n=49, mean age 5.6 ± 3.3 | Admission rate:<br><br>7% HS, 22/52 (42.3%)<br><br>0.9% NS, 24/49 (49%) |
| Khanal et al, 2015, Nepal | 3% HS compared to 0.9% NS inhalations twice, both HS and NS 4mL with epinephrine administered twice | Infants between six weeks and 24 months of age<br><br>3% HS, n=50, mean age 9.82 ± 5.06<br><br>0.9% NS, n=50, mean age 9.51 ± 4.28 | Admission rate:<br><br>3% HS, 15/50 (30%)<br><br>0.9% NS, 35/50 (70%) |
| Wu et al, 2014, USA | 3% HS compared to 0.9% NS inhalations every 20 minutes until three doses, both HS and NS 4mL and given after albuterol inhalation | Infants under 24 months of age<br><br>3% HS, n=231, mean age 6.57 ± 5.17<br><br>0.9% NS, n=216, mean age 6.40 ± 5.33 | Admission rate:<br><br>3% HS, 61/231 (26.4%)<br><br>0.9% NS, 84/216 (38.9%) |

# ORIGINAL PUBLICATIONS

I        Heikkilä P, Forma L, Korppi M. Hospitalisation costs for infant bronchiolitis are up to 20 times higher if intensive care is needed. *Acta Paediatr. 2015;104:269-273.*

II       Heikkilä P, Forma L, Korppi M. High-flow oxygen therapy is more cost-effective for bronchiolitis than standard treatment - a decision-tree analysis. *Pediatr Pulmonol. 2016;51:1393-1402.*

          Heikkilä P, Forma L, Korppi M. Erratum: High-flow oxygen therapy is more cost-effective for bronchiolitis than standard treatment - A decision-tree analysis. *Pediatr Pulmonol. 2017 DOI:10.1002/ppul.23660*

III      Heikkilä P, Mecklin M, Korppi M. The cost-effectiveness of hypertonic saline inhalations for infant bronchiolitis: a decision analysis. *World Journal of Pediatrics, in press.*

IV      Heikkilä P, Renko M, Korppi M. Hypertonic saline inhalations in infant bronchiolitis – a cumulative meta-analysis. *August 2017 (Submitted).*

**REGULAR ARTICLE**

# Hospitalisation costs for infant bronchiolitis are up to 20 times higher if intensive care is needed

Paula Heikkilä (paula.heikkila@uta.fi)[1,2], Leena Forma[1], Matti Korppi[2]

1.School of Health Sciences, University of Tampere, Tampere, Finland
2.Center for Child Health Research, University of Tampere and Tampere University Hospital, Tampere, Finland

## ABSTRACT

**Aim:** Up to 3% of infants with bronchiolitis under 12 months of age are hospitalised, and up to 9% require intensive care. We evaluated the costs of bronchiolitis hospitalisation, with a special focus on whether infants needed intensive care.

**Methods:** Baseline and cost data were retrospectively collected, using electronic hospital files, for 80 infants under 12 months old who were treated in the paediatric intensive care unit (PICU) for bronchiolitis during a 13-year period. We calculated the daily costs for patients admitted to the PICU and compared them with 104 admitted to inpatient wards and 56 outpatients treated in the emergency department.

**Results:** The mean hospitalisation cost for PICU patients was €8061 (95% CI 6193–9929), compared to €1834 (1649–2020) for other inpatients and €359 (331–387) for the outpatients. The hospitalisation cost per patient was associated with length of hospital stay, but not gender, age on admission or gestational age. There was no constant increase or decrease in hospitalisation costs during the study period.

**Conclusion:** The hospitalisation costs of infants treated in the PICU for bronchiolitis at <12 months of age were approximately four times more than for other inpatients and over 20 times more than for outpatients. Strategies are needed to reduce the need for intensive care.

Bronchiolitis is usually defined as the first virus-induced episode of respiratory distress, with or without wheezing, at <12 months of age (1) and is the most common infection requiring hospital care in Western infants (2). About 1–3% infants are treated for bronchiolitis in hospital during the first year of life (3) and 8–9% of them need intensive care (4,5). Respiratory syncytial virus (RSV) is the predominant causative agent.

The main complications associated with infant bronchiolitis are hypoxaemia and dehydration. Therefore, the cornerstones of bronchiolitis treatment are close monitoring of breathing work, oxygen saturation and fluid intake and, when needed, oxygen administration, fluid supplementation or respiratory support (2). The role of drug therapy is minor, as inhaled adrenalin may offer transient resolution of bronchial obstruction, but other medicines such as beta-agonists and corticosteroids are not effective (2,3,6,7). If the infants are at risk of respiratory insufficiency, they need to be treated in the paediatric intensive care unit (PICU).

**Abbreviations**

CI, Confidence interval; ED, Emergency department; LOS, Length of stay; NordDRG, Nordic Diagnosis Related Groups; PICU, Paediatric intensive care unit; RSV, Respiratory syncytial virus.

Infants who are <3 months old were born premature, and in particular, those with bronchopulmonary dysplasia are at the greatest risk.

Although the burden of disease caused by bronchiolitis is major, there are only a few reports summarising the economic burden. In the USA, annual total hospital charges for bronchiolitis were estimated to be US$1.64–1.83 billion in 2009 (8). In Germany, direct annual costs caused by lower respiratory infections in young children were estimated to be €213 million in 2002 (9). The annual emergency department (ED) costs for bronchiolitis in Spain were €20 million in 2011 (10). In addition, bronchiolitis or

**Key notes**

- Up to 3% of infants with bronchiolitis under 12 months of age are hospitalised, and up to 9% of them require intensive care.
- The mean hospitalisation costs per patient were €8061 if intensive care was needed, but substantially less for those treated on the ward (€1834) and in the emergency department (€359).
- New strategies are required to reduce hospital stays and costs, by decreasing the need for intensive care for bronchiolitis.

pneumonia in infancy leads to additional healthcare costs in the year after infection (11). Corresponding data are not available from the Nordic countries. Therefore, we charted the costs of bronchiolitis treatment in infants under 12 months old requiring treatment in the PICU of Tampere University Hospital between 2000 and 2012.

The aims of this retrospective study were to evaluate the cost of hospitalisation for bronchiolitis, the factors associated with high costs and the differences in costs between infants who were treated in the PICU, on the ward and in the ED of the hospital. We also studied the annual variations and possible trends in costs during the study period.

## MATERIAL AND METHODS

### Design

We carried out a retrospective review of the electronic patient files of Tampere University Hospital, Tampere, Finland. The hospitalisation and associated costs of the infants treated in the PICU were compared to the costs of those treated as inpatients on the ward or as outpatients in the ED. Because the patients were not contacted by the researchers, the study was carried out with the permission of the Chief Physician of the University Hospital.

Tampere University Hospital is located in Central South-West Finland and is the only hospital providing inpatient care for a population of about 90 000 children under 16 years old. The population of infants under 12 months old was 5045 in 2000 and 6065 in 2012. In addition, Tampere University Hospital provides paediatric intensive care for patients from four surrounding central hospitals.

We identified 80 infants who were treated for bronchiolitis under 12 months of age in the PICU in 2000–2012 from the electronic register of the hospital. For each PICU case, we selected two controls who had been diagnosed with bronchiolitis just before or after the case and were treated as an inpatient on the ward (n = 104) or as an outpatient in ED (n = 56).

One of the authors (PH) collected the cost data and the basic and medical data for the cases and controls using a structured form, including admission and departure dates and times, gestational age (full-term ≥37 weeks, preterm <37 weeks or <32 weeks), gender, age on hospital admission and presence of bronchopulmonary dysplasia, doctor-diagnosed asthma in parents or siblings, or doctor-diagnosed allergy, such as atopic dermatitis or food allergy, in the infants. Length of hospital stay (LOS) was calculated separately for treatment in the PICU and on the ward and was summarised as total LOS.

### Cost data

Cost data were collected from the healthcare providers' perspective. The electronic data that were available consisted of daily municipal billing for every patient, which was based on expense categories from 2000 to 2006 and on either expense categories or Nordic Diagnosis Related Groups (NordDRG) categories from 2007 to 2012 (Table S1). The costs of each day were invoiced separately for each patient, and the invoice for the day was determined based on the expense category or on the Nordic Diagnosis Related Groups' (NordDRG) category of that day. In principle, the costs should be identical, but no comparisons have been carried out between the two categories. The costs were calculated separately for the ED, ward and PICU expenditures. The costs that were included were the real municipal billing sums for every patient, and no average sums or calculated estimates were used. The doctor who was responsible for the treatment of the patient defined the expense or NordDRG category separately for each day, depending on how demanding the treatment was and how expensive the examinations were.

The expense and NordDRG categories were constructed to cover all expenses in the hospital such as medication, other treatments, different procedures, diagnostic tests, staff salaries and even property overheads. These categories did not include indirect expenses, such as costs incurred by the families or even by the third payers such as employers. Costs were expressed as Euros and transformed into year 2012 levels using the Association of Finnish Local and Regional Authorities' hospital financing index.

When the costs were compared between Finland and the USA, we used the rate of €1 = US $1.3615.

### Statistics

Statistical analyses were performed with SPSS 21 software (SPSS Inc., Chicago, IL, USA). Exploratory data analysis revealed that the costs were non-normally distributed. Analyses were carried out for the total costs per patient and the costs per day per patient when appropriate.

For costs per patient, Spearman's correlation and analysis of variance were used for continuous variables and the chi-square test and the Mann–Whitney $U$-test were used for categorised variables in the univariate analyses.

Linear regression analysis with logarithmic transformation was used for costs per patient per day in the PICU group in the univariate analyses. It was also used in multivariate analyses, with treatment year, age on admission, gestational age, gender, allergy, family asthma and length of PICU stay as covariates.

The results are expressed as proportions, means, 95% confidence intervals (95% CI) and ranges. A p-value of <0.05 was considered as statistically significant.

## RESULTS

The mean age of the 80 infants treated in the PICU for bronchiolitis at <12 months of age was 13 weeks, compared to 21 weeks in the control groups (p < 0.001), and the mean gestational age was 34.6 weeks, compared to 38.7 in the control groups (p < 0.001). Nearly half of the patients were born before 37 weeks and 27.5% at <32 weeks of gestation (Table 1). The annual numbers of infants treated in the PICU for bronchiolitis varied between 0 in 2006–14 in 2001.

Total length of stay (LOS) and costs per patient could not be calculated for the 13 infants (16.3%) who were transferred to the PICU from other hospitals. In the control

groups, 56 were treated in the ED and 104 on the ward. The mean total LOS was 10 days (95% CI 8.1–11.2) in the PICU group – with a mean stay of 4.6 days in the PICU and 4.7 days on the ward – compared to 3 days in the 104 inpatient controls (Table 2).

The mean hospitalisation costs for infants treated in the PICU were €8061 (95% CI €6193–9929) (Table 3). The mean daily costs were €768 for PICU patients: €961 in the PICU, €533 on the ward and €223 in the ED. The mean ward costs of the inpatient controls (€1587) were 44% of the cost of the cases (€3577), but the costs per day were equal (Table 3).

In the PICU group, the mean hospitalisation costs per patient were €6337 (95% CI €3929–8745) in those born after 37 weeks of gestation, €10 108 (€6980–13 237) in those born before 37 weeks of gestation and €10 575 (€7556–13 595) in those born at <32 weeks of gestation. The costs per patient per day in these three gestational age-based groups were €677 (95% CI 576–777), €853 (743–963) and €923 (775–1071), respectively.

The hospitalisation costs per patient correlated strongly with the total LOS (r = 0.960; p < 0.001) and length of PICU stay (r = 0.681; p < 0.001). There was a weaker link with gestational age (r = −0.346, p < 0.001) and age on hospital admission (r = −0.344, p < 0.001).

In the univariate linear regression, treatment year (r = 0.37), gestational age (r = 0.36) and length of PICU stay (r = 0.45) showed a statistically significant association with the costs per patient per day in the PICU group (Table 4). In the multivariate linear regression, gestational age lost statistical significance, but treatment year and length of PICU stay retained statistical significance (Table 4).

In the PICU group, the mean hospitalisation costs per patient were more than €8000 in 2000, 2001, 2005, 2009 and 2012, with no significant increases or decreases constantly from year to year (Figure S1). The mean costs per patient per day in the PICU were highest (over €1000) in 2000, 2001, 2002, 2005 and 2008, again with no constant increases or decreases from year to year (Figure S2).

We estimated the cost of bronchiolitis hospitalisation at the national level using the current mean costs per patient – €8061 in those treated in the PICU and €1834 in those treated on the ward. We assumed that 1% or 3% of all infants were hospitalised for bronchiolitis and that 10% of them were treated in the PICU. In Finland, the number of infants under 12 months old is about 60 000. With the rate of 1%, 600 infants would be hospitalised and 60 would be treated in the PICU and the calculated hospitalisation costs for bronchiolitis would be €1 474 020 (95% CI 1 262 040–1 686 540). With the rate of 3%, 1800 infants would be hospitalised and 180 would be treated in the PICU and the calculated hospitalisation costs for bronchiolitis would be €4 422 060 (€3 786 120–5 059 620).

## DISCUSSION

The mean hospitalisation costs per patient for infants of <12 months old who were treated in the PICU for bronchiolitis were more than four times higher than for those treated as inpatients on the ward and over 20 times higher than for those treated as outpatients in the ED. We estimated that the annual direct total hospitalisation costs of bronchiolitis at <12 months of age were €1.5 million to €4.4 million in Finland, a country with a population of 5.4 million people.

In multivariate analyses, the length of PICU stay and hospitalisation year were the only independently significant factors for higher hospitalisation costs in the PICU group. The annual numbers of bronchiolitis patients, and hence the hospitalisation costs, varied substantially, but there were no consistent trends in the costs per patient or per

**Table 1** Basic characteristics of the 80 infants treated for bronchiolitis in the paediatric intensive care unit and the 160 controls treated on the ward or emergency department of the hospital at <12 months of age

|  | Cases n = 80 | Controls n = 160 | p |
|---|---|---|---|
| Gender (boys) no (%) | 47 (58.8) | 93 (58.1) | 0.926 |
| Age (weeks) mean (95% CI) | 13 (10–15) | 21 (19–24) | <0.001 |
| Gestational age mean (95% CI) | 34.6* (33.3–35.8) | 38.7† (38.3–39.1) | <0.001 |
| <37 weeks no (%) | 36* (49.3) | 19† (12.1) | <0.001 |
| <32 weeks no (%) | 22* (27.5) | 2† (1.3) | <0.001 |
| BPD no (%) | 7 (8.8) | 1 (0.6) | 0.001 |
| Allergy no (%) | 3* (38.9) | 10 (6.3) | 0.456 |
| Family asthma no (%) | 8 (10) | 25 (15.6) | 0.233 |

BPD = Bronchopulmonary dysplasia; 95% CI = 95% Confidence interval.
Missing data in three cases* and in seven controls†.
Allergy is defined as doctor-diagnosed atopic dermatitis or food allergy in infants.

**Table 2** Length of stay (days) of the cases on the ward plus intensive care unit and of the inpatient controls on the ward

|  | No (%) | Ward mean (95% CI) | Range | PICU mean (95% CI) | Range | Total mean (95% CI) | Range |
|---|---|---|---|---|---|---|---|
| PICU patients (cases) | 80 (33.3) | 4.7* (3.3–6.0) | 0–33 | 4.6 (3.6–5.6) | 1–27 | 10* (8.1–11.2) | 1–38 |
| Inpatient controls | 104 (43.3) | 3 (2.7–3.5) | 1–12 | – | – | 3 (2.7–3.5) | 1–12 |
| Outpatient controls | 56 (23.3) | – | – | – | – | – | – |

PICU = Paediatric intensive care unit.
*n = 67.

**Table 3** Hospitalisation costs per patient and per patient per day, presented separately for cases and inpatient and outpatient controls

|  | PICU patient (n = 80) mean (95% CI) | Range | Inpatient (n = 104) mean (95% CI) | Range | Outpatient (n = 56) mean (95% CI) | Range |
|---|---|---|---|---|---|---|
| Costs/patient |  |  |  |  |  |  |
| ED | 236 (216–255)* | 182–624 | 248 (231–264) | 182–650 | 359 (331–387) | 210–562 |
| Ward | 3577 (2437–4718)† | 266–23 193 | 1587 (1402–1771) | 419–4802 |  |  |
| PICU | 4877 (3560–6194) | 0–34 150 |  |  |  |  |
| Total | 8061 (6193–9929)‡ | 1122–43 437 | 1834 (1649–2020) | 747–5021 | 359 (331–387) | 210–562 |
| Costs/day |  |  |  |  |  |  |
| ED | 223 (212–237) | 182–416 | 232 (222–243) | 182–420 | 359 (331–387) | 210–562 |
| Ward | 533 (478–565) | 98–1013 | 556 (524–588) | 277–1327 |  |  |
| PICU | 961 (739–983) | 0–1823 |  |  |  |  |
| Total | 768 (625–770) | 306–1517 | 677 (636–719) | 322–1536 | 359 (331–387) | 210–562 |

PICU = Paediatric intensive care unit; ED = Emergency department.
*n = 60.
†n = 61.
‡n = 67.

**Table 4** Linear regression: factors associated with hospitalisation costs per patient per day in the 80 infants treated for bronchiolitis in the paediatric intensive care unit

|  | Univariate B (seB) | p | $r^2$, % | Multivariate B (seB) | p | $r^2$, % |
|---|---|---|---|---|---|---|
| Gestational age | −0.012 (0.004) | 0.004 | 13.1 | −0.009 (0.004) | 0.053 | 37.3 |
| Age (weeks) | 0.000 (0.002) | 0.821 | 0.1 | 0.000 (0.002) | 0.903 |  |
| Gender | 0.016 (0.043) | 0.707 | 0.2 | −0.003 (0.041) | 0.952 |  |
| Allergy | −0.074 (0.104) | 0.481 | 0.8 | 0.021 (0.113) | 0.855 |  |
| Family asthma | −0.027 (0.066) | 0.680 | 0.3 | −0.016 (0.072) | 0.821 |  |
| PICU stay | 0.17 (0.004) | 0.000 | 20.1 | 0.012 (0.005) | 0.017 |  |
| Treatment year | −0.016 (0.005) | 0.002 | 14.0 | −0.017/0.005 | 0.001 |  |

PICU = Paediatric intensive care unit.

patient per day during the 13-year surveillance period. Being <3 months old has been identified as a risk factor for severe bronchiolitis (2) and preterm-born infants are at higher risk of needing intensive care than those born full-term (2,12,13). In the present study, the mean age of the PICU patients was lower than the controls and 49% of them were born before 37 weeks of gestation, compared to 12% of the controls and 4.2% of the Finnish population (14). However, age was not associated with hospitalisation costs in the PICU group and the association between costs and gestational age was only suggestive.

The coefficient of determination of the multivariate linear regression model was 37.3%, which is acceptable. On the other hand, it means that 62.7% of the variation of costs between the groups were caused by factors other than those included in the model. As the population in Finland is rather socially and economically homogenous, it is unlikely that the inclusion of social or economic parameters had made the model substantially better. Instead, early-life exposure to tobacco smoke could have been a factor. Parental smoking, especially maternal smoking during pregnancy, is a well-known risk factor for severe bronchiolitis (13), but it was not possible to retrospectively collect detailed parental smoking data from the hospital records.

In the USA, the annual total direct costs of bronchiolitis hospitalisation were $US545 million in 2009 (8), which

were, in relation to the respective populations, 1.5- to 4.2-fold higher than our estimates for Finland. The American mean costs per hospitalisation varied from $US3208 to $US6191, depending on comorbidities (15) and those estimates were 1.7- to 3.4-fold higher than the average hospitalisation costs per patient in the present Finnish study.

In Germany, the mean costs of inpatient treatment of RSV infections were € 2772 (9) in 2002, compared to €1587 in the present study on bronchiolitis treatment for infants of <12 months old.

In an American study, lower respiratory infection caused by RSV, such as infant bronchiolitis, led to significantly higher healthcare use and costs during the subsequent year when compared to controls who did not have an earlier RSV infection (11). The marginal costs among inpatient preterm infants with RSV infection were $US34 132, and among outpatient full-term infants with RSV infection, they were $US1428, compared to controls without RSV infection (16).

In recent years, nasal continuous positive airway pressure has been actively used in the treatment of severe infant bronchiolitis, which has led to less intensive care, shorter stays in hospital and lower hospitalisation costs (17). High-flow nasal oxygenation with warmed and humidified oxygen–air mixture (Optiflow) is the newest treatment modality

for noninvasive respiratory support (18,19). Both treatments can be carried out in the paediatric ward, which will lessen the need for intensive care.

Prophylaxis with palivizumab, an RSV-specific humanised immunoglobulin, has been cost-effective in decreasing RSV hospitalisation and the need for intensive care in preterm infants (20). Usually, infants born before 32 weeks of gestation have been treated during RSV epidemics until 12 months of age (21). In the present study, 27.5% of the patients were born before 32 weeks of gestation and their hospitalisation costs accounted for 36% of the cost of the whole PICU group.

Only a few studies have reported bronchiolitis costs from the families' perspective. According to Dutch (22) and Spanish studies (10), 15.5–16.8% should be added to the direct healthcare costs incurred by the healthcare provider to cover the costs incurred by the families. These include factors such as the parent's lost working days, visits to the doctor, day care for other children, travelling between home and the hospital and buying medicines (22). This would mean that the annual total costs of bronchiolitis hospital treatment in Finland would be between €1.7 million and €5.5 million.

## CONFLICTS OF INTEREST
None.

## References

1. Smyth R, Openshaw P. Bronchiolitis. *Lancet* 2006; 368: 312–22.
2. American Academy of Pediatrics (AAP). Diagnosis and management of bronchiolitis. *Pediatrics* 2006; 118: 1774–93.
3. Øymar K, Skjerven H, Bruun Mikaelsen I. Acute bronchiolitis in infants, a review. *Scand J Trauma Resusc Emerg Med* 2014; 22: 23–33.
4. Behrendt C, Decker M, Burch D, Watson P, the International RSV Study Group. International variation in the management of infants hospitalized with respiratory syncytial virus. *Eur J Pediatr* 1998; 157: 215–20.
5. Leader S, Kohlhase K. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. *J Pediatr* 2003; 143: S127–32.
6. Fernandes RM, Bialy LM, Vandermeer B, Tjosvold L, Plint AC, Patel H, et al. Glucocorticoids for acute viral bronchiolitis in infants and young children. *Cochrane Database Syst Rev* 2013; 6: CD004878.
7. Zorc J, Hall C. Bronchiolitis: recent evidence on diagnosis and management. *Pediatrics* 2010; 125: 342–9.
8. Hasewaga K, Tsugawa Y, Brown D, Mansbach J, Camargo C. Trends in bronchiolitis hospitalizations in the United States, 2000–2009. *Pediatrics* 2013; 132: 28–36.
9. Ehlken B, Ihorst G, Lippert A, Petersen G, Schumacher M. Economic impact of community-acquired and nosocomial lower respiratory tract infections in young children in Germany. *Eur J Pediatr* 2005; 164: 607–15.
10. Garcia-Marcos L, Valverde-Molina J, Pavlivic-Nesic S, Claret-Teruel G, Peñalba-Citores A, Nehme-Álvarez D, et al. Pediatricians' attitudes and costs of bronchiolitis in the emergency department: a prospective multicentre study. *Pediatr Pulmonol* 2014; 49: 1011–9.
11. Palmer L, Hall C, Katkin J, Shi N, Masaquel A, McLaurin K, et al. Healthcare cost within a year of respiratory syncytial virus among Medicaid infants. *Pediatr Pulmonol* 2010; 45: 772–81.
12. National Institute of Health and Welfare. New Born 2012 – Statistical Report. Available from: URL: http://www.julkari.fi/bitstream/handle/10024/110752/Tr32_13.pdf?sequence=4.
13. Hervás D, Reina J, Yañez A, del Valle JM, Figuerola J, Hervás JA. Epidemiology of hospitalization for acute bronchiolitis in children: differences between RSV and non-RSV bronchiolitis. *Eur J Clin Microbiol Infect Dis* 2012; 31: 1975–81.
14. Nagakumar P, Doull I. Current therapy of bronchiolitis. *Arch Dis Child* 2012; 97: 827–30.
15. Pelletier A, Mansbach J, Camargo C. Direct medical costs of Bronchiolitis hospitalizations in the United States. *Pediatrics* 2006; 118: 2418–23.
16. Shi N, Palmer L, Chu B-C, Katkin J, Hall C, Masaquel A, et al. Association of RSV lower respiratory tract infection and subsequent healthcare use and costs: a Medicaid claims analysis in early-preterm, late-preterm, and full-term infants. *J Med Econ* 2011; 14: 335–40.
17. Essouri S, Laurent M, Chevret L, Durand P, Ecohard E, Gajdos V, et al. Improved clinical and economic outcomes in severe bronchiolitis with pre-emptive nCPAP ventilator strategy. *Intensive Care Med* 2014; 40: 84–91.
18. McKiernan C, Chua L, Visintainer P, Allen H. High flow nasal cannulae therapy in infants with bronchiolitis. *J Pediatr* 2010; 156: 634–8.
19. Schibler A, Pham T, Dunster K, Foster K, Barlow A, Gibbons K, et al. Reduced intubation rates for infants after introduction of high-flow nasal prong oxygen delivery. *Intensive Care Med* 2011; 37: 847–52.
20. Andabaka T, Nickerson J, Rojas-Reyes M, Rueda J, Bacic Vrca V, Barsic B. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children (Review). *Cochrane Libr* 2013; 4: 1–131.
21. American Academy of Pediatrics (AAP). Modified recommendations for use of prevention of respiratory syncytial virus infections. *Pediatrics* 2009; 124: 1694–701.
22. Miedema C, Kors A, Tjon A Ten W, Kimpen J. Medical consumption and socioeconomic effect of infection with respiratory syncytial virus in the Netherlands. *Pediatr Infect Dis J* 2001; 20: 160–3.

## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Table S1** Expense categories in 2012.
**Figure S1** Mean annual hospitalisation costs per patient in infants treated for bronchiolitis in the paediatric intensive care unit during the 13-year study period.
**Figure S2** Mean annual hospitalisation costs per patient per day in infants treated for bronchiolitis in the paediatric intensive care unit during the 13-year study period.

# High-Flow Oxygen Therapy is More Cost-Effective for Bronchiolitis Than Standard Treatment—A Decision-Tree Analysis

Paula Heikkilä, MSc,[1]* Leena Forma, PhD,[2] and Matti Korppi, MD, PhD[1]

**Summary.** We evaluated the cost-effectiveness of high-flow nasal cannula (HFNC) to provide additional oxygen for infants with bronchiolitis, compared to standard low-flow therapy. The cost-effectiveness was evaluated by decision analyses, using decision tree modeling, and was based on real costs from our recently published retrospective case-control study. The data on the effectiveness of HFNC treatment were collected from earlier published retrospective studies, using admission rates to pediatric intensive care units (PICU). The analyses in the study showed that the expected treatment costs of each episode of infant bronchiolitis varied between €1,312–2,644 ($1,786–3,600) in the HFNC group and €1,598–3,764 ($2,175–5,125) in the standard treatment group. The PICU admission rates and consequential costs were lower for HFNC than for standard treatment. HFNC treatment proved more cost-effective than standard treatment in all the baseline analyses and was also more cost-effective in the sensitivity analyses, except for in the worst-case scenario analysis. In conclusion, our modeling demonstrated that HFNC was strongly cost-effective for infant bronchiolitis, compared to standard treatment because it was both more effective and less expensive. Thus, if children hospitalized for bronchiolitis need oxygen, it should be delivered as HFNC treatment. **Pediatr Pulmonol. 2016;51:1393–1402.** © 2016 Wiley Periodicals, Inc.

Key words: bronchiolitis; hospitalization costs; high-flow nasal cannula; cost-effectiveness; decision analysis.

## INTRODUCTION

Bronchiolitis is a significant public health problem in infants, as both the disease burden and treatment costs are high.[1,2] Respiratory syncytial virus (RSV) is the most common causative agent in infant bronchiolitis[3] and about 1–3% of each age cohort are treated in hospital for RSV or other viral respiratory infections.[3] The need for intensive care has been reported to vary from 6% to 17% of infants hospitalized for bronchiolitis.[4–7]

The main physiological problem associated with bronchiolitis is disturbed gas exchange, often leading to hypoxemia.[3,8] Therefore, the cornerstone of treatment is close monitoring of oxygen saturation and supplementary oxygen administration, if needed.[8–10]

If there is a threat of respiratory failure, the patient needs ventilatory support such as nasal continuous positive airways pressure (nCPAP) therapy or even artificial ventilation. In most hospitals, such ventilatory support is carried out in the pediatric intensive care unit (PICU). In our recent study of 80 infants of less than 12 months-of-age treated in the PICU for bronchiolitis, the hospitalization costs were four times more than in those treated for bronchiolitis on the pediatric ward and over 20 times more than in those treated in the emergency department (ED).[11]

Administering a mixture of warmed humidified oxygen and air through a high-flow nasal cannula (HFNC) is a

[1]Tampere Center for Child Health Research, University of Tampere and Tampere University Hospital, Tampere, Finland.

[2]School of Health Sciences, University of Tampere, Tampere, Finland.

Conflicts of interest: None.

*Correspondence to: Paula Heikkilä, MSc, Tampere University Hospital, Department of Pediatrics, PO Box 2000, FI-33521 Tampere, Finland. E-mail paula.heikkila@uta.fi

promising new way of treating infants with bronchiolitis.[12–15] Studies have reported that HFNC decreased the need for intubation and intensive care for infants hospitalized for bronchiolitis, but results were based on comparisons with historical controls[12,14,15] or on very small sample sizes in a prospective pilot study.[13] Other studies have reported that HFNC offered many beneficial physiologic effects when treating bronchiolitis, but these studies were observational with small numbers of patients.[16–19]

Health economic research is important as it helps to achieve the best health utility by allocating available resources effectively[20] and cost-effectiveness analyses compare the costs and effectiveness of different interventions. Decision analysis is a mathematical modeling used to measure cost-effectiveness in health economic research.[21] It provides a systematic quantitative approach for comparing two or more different treatment modalities[20] and is useful when variability and uncertainty are associated with all decisions. Decision models can be constructed to combine different data and decision analysis aims to create a synthesis for decision problems.[21]

This study used the decision analysis method to evaluate whether using HFNC to provide oxygen for infants with bronchiolitis who require additional oxygen could cut hospitalization costs by reducing the need for PICU admissions. We estimated the cost of providing infants with bronchiolitis with HFNC treatment based on true hospitalization costs in our recent study and on the published effectiveness of HFNC treatment over standard supportive care. As the available data on HFNC effectiveness was based on comparisons with historical controls, the actual effectiveness was not known and the cost-effectiveness threshold was evaluated using different levels of effectiveness.

## MATERIALS AND METHODS

### Design

We used the decision tree model to compare the cost-effectiveness of HFNC treatment with standard supportive treatment. The presumptive levels of the effectiveness of HFNC treatment were obtained from previously published studies comparing children treated with a HFNC with historical controls.[14,15] Effectiveness was measured using rates of PICU admissions and the cost of treatment in the PICU and on the pediatric ward were obtained from our recent study.[11]

### Literature Research

We searched PubMed for publications on HFNC treatment in infants with bronchiolitis up to January 2015, using the search terms "bronchiolitis" and "high and/or flow and/or nasal and/or cannula" or "ventilatory and/or support." Our search identified 96 studies, and we selected 38/96 after reading the title, 12/38 after studying the abstract and four after reading the full paper. Two were from the US[12,14] and two were from Australia.[13,15] Three studies were retrospective chart reviews comparing the periods before and after the introduction of HFNC treatment[12,14,15] and one was a prospective pilot study whose principal aim was to find the optimal flow rate of oxygen-air mixture compared with standard low-flow nasal oxygen administration.[13]

### Decision Analysis Model

Statistical analyses were performed with TreeAge Pro version 2015 (TreeAge Software, Inc., MA, Williamstown). We used the decision tree as the decision analysis model. Model 1 was constructed using the real mean total cost of the hospitalization and the probabilities of PICU treatment as variables and the effectiveness of the treatment as the effect outcome (Fig. 1). Model 2 was constructed using the mean cost per day multiplied by the length of hospital stay (LOS), the probability of PICU admission, and the different ventilatory supports that were needed as variables, and the effectiveness of the treatment as the effect outcome (Fig. 2). The analyses were carried out using the rollback technique. Only inpatient costs were included in the analyses. The model endpoint at all branches was the discharge of the patient.

### Effectiveness of HFNC in Previous Studies

The details of the four bronchiolitis studies we included are summarized in Table 1. When HFNC was used, the intubation rate reduced from 23% to 9% in 115 infants[14] and from 37% to 7% in 167 infants,[15] respectively, and the need for intensive care reduced from 31% to 13% in 93 infants.[13] In the American study, HFNC failed in 15/231 infants, which means that 6.5% of the patients treated with HFNC needed intubation.[12] In the Australian study, only 4% of the patients treated with HFNC needed intubation, but as many as 25% needed other forms of non-invasive respiratory support.[15] HFNC treatment did not shorten the LOS in the only prospective pilot study.[13]

---

ABBREVIATIONS

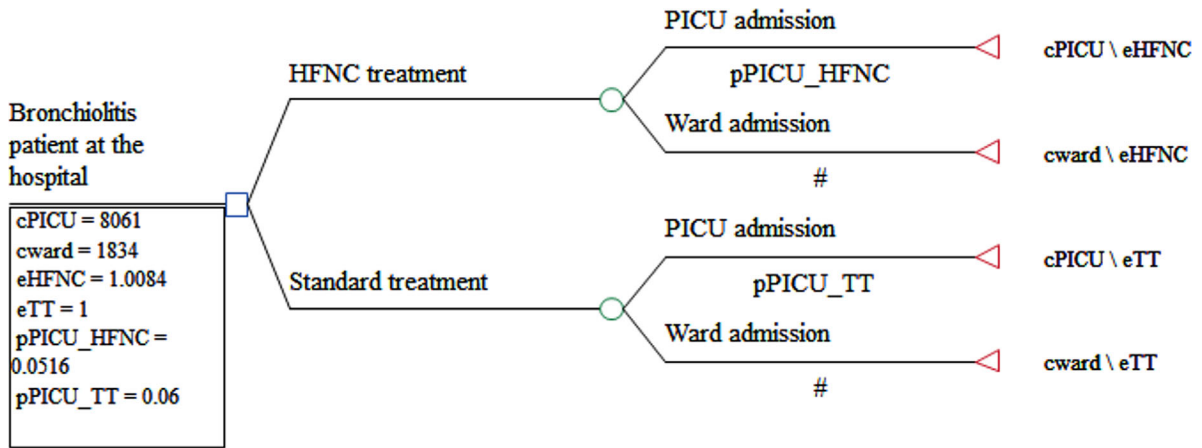| | |
|---|---|
| E | Effectiveness |
| ED | Emergency department |
| HFNC | High-flow nasal cannula |
| ICER | Incremental cost-effective ratio |
| LOS | Length of stay |
| nCPAP | Nasal continuous positive airways pressure |
| P | Probability |
| PICU | Pediatric intensive care unit |
| RSV | Respiratory syncytial virus |
| WCSA | Worst-case scenario analyses |

**Fig. 1. The decision tree for Model 1. Prefix p indicates probability, c indicates cost as Euros, and e indicates effectiveness. PICU, pediatric intensive care unit; HFNC, high-flow nasal cannula treatment, ST, standard treatment.**

## Probabilities

In decision analysis modeling, we presumed that the PICU admission rate was 6% among infants hospitalized for bronchiolitis if the standard therapy without HFNC was used, as recently seen in a Finnish prospective[4] and a retrospective study.[5] When we estimated the probability of PICU admission when HFNC was used, we presumed that the PICU admission rate would reduce as much as HFNC therapy reduced the intubation rate. This hypothesis
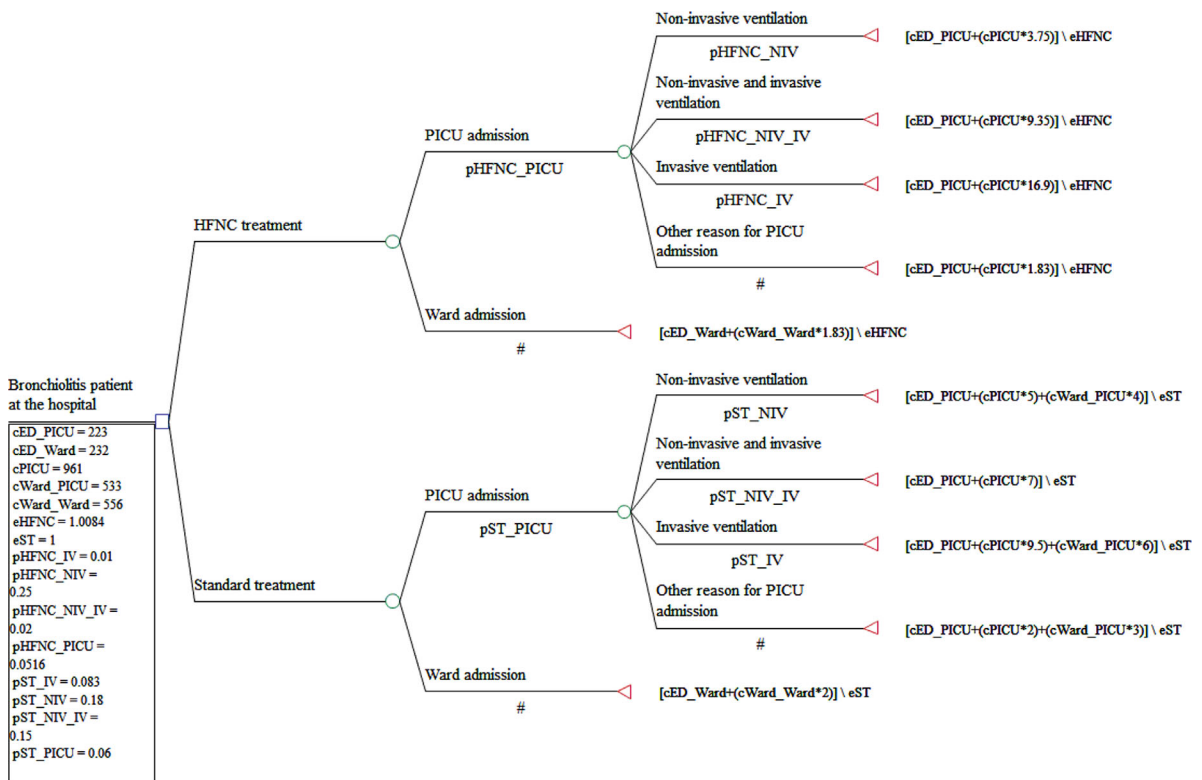


**Fig. 2. The decision tree for Model 2. Prefix p indicates probability, c indicates cost as Euros, and e indicates effectiveness. PICU, pediatric intensive care unit; ED, emergency department; HFNC, high-flow nasal cannula treatment, ST, standard treatment; NIV, non-invasive ventilation; IV, invasive ventilation.**

**TABLE 1—Previous Studies on the Effects of High Flow Nasal Cannula (HFNC) Treatment**

| Basic study details | The study protocol | Main results |
|---|---|---|
| Mayfield et al.[13] Australia | Prospective controlled pilot study, including 61 cases treated with HFNC admitted to the ward and 33 retrospectively selected controls treated on the ward at the same time as cases | In the HFNC group, eight (13%) patients were admitted to the PICU, compared to 10 (31%) in the standard treatment group |
| | Infants hospitalized for bronchiolitis at less than 12 months of age | LOS and the length of treatment did not differ between the groups |
| | Comparison of the treatment effects between HFNC and standard treatment groups | |
| Kelly et al.[12] USA | Retrospective chart review of 231 infants hospitalized for bronchiolitis at less than 24 months of age | In infants treated with HFNC, the intubation rate was 15/231 (6.5%) |
| | Evaluation of patient characteristics that predict success or failure of HFNC | |
| Schibler et al.[15] Australia | Retrospective chart review of 167 infants hospitalized in the PICU for bronchiolitis at less than 24 months of age | HFNC reduced the need for intubation from 37% to 7%. However, 25% of infants needed other non-invasive ventilation support |
| | Comparison of the treatment effectiveness before and after using HFNC | Median LOS was 1.83 d (HFNC), 3.75 (HFNC + NIV), 9.35 (HFNC + NIV + IV) and 16.9 (HFNC + IV) |
| McKiernan et al.[14] USA | Retrospective chart review of 115 infants hospitalized in the PICU for bronchiolitis at less than 24 months of age | HFNC reduced the need for intubation from 23% to 9% |
| | Comparison of the treatment effectiveness before and after using HFNC | PICU stay was reduced from 6 to 4 days ($P = 0.0058$) |

LOS, length of hospital stay; HFNC, high-flow nasal cannula; NIV, non-invasive ventilation; IV, invasive ventilation.

supposes that HFNC patients can be treated on the pediatric ward but infants who need ventilation are treated in the PICU. Thus, the reduction of the intubation rate in this model from 23% to 9%, or from 37% to 7%, meant that the 14% or 30% of the patients who were not intubated could have been treated on the ward, leading to a respective reduction in the need for PICU treatment. The probability of PICU admission in infants hospitalized for bronchiolitis was calculated using the equation

$$P = y - \frac{y \times \int b - y \times \int a}{100}$$

where $P$ is the probability of the PICU admission (%), y is the PICU admission rate before HFNC, $\int b$ is the intubation rate when HFNC was not in use, and $\int a$ is the intubation rate when HFNC was in use.

The frequency with which other methods of ventilatory support were used in patients treated with HFNC were obtained from Schibler et al.,[15] again on the assumption that HFNC treatment could be given on a pediatric ward. The rates for those treated without HFNC were obtained from our own study (unpublished data) (Table 2). The other ventilatory support groups were only non-invasive ventilation (only NIV), only invasive ventilation (only IV) and both (NIV and IV). Bronchiolitis patients who needed PICU treatment without ventilatory support (Table 2), formed the fourth group in our model.

**Effectiveness**

The reduction of PICU admission rates for bronchiolitis was used to measure the effectiveness of HFNC treatment, using the equation

$$E = 1 + \frac{y - P}{100}$$

where E is the effectiveness of HFNC treatment, $P$ is the probability of PICU admission (%), and y is the PICU admission rate without HFNC treatment. The comparable effectiveness was set at one.

**Cost Data**

Cost data were obtained from the real costs of our recent retrospective study.[11] In brief, we identified 80 infants who were treated for bronchiolitis at less than 12 months of age in the PICU at Tampere University Hospital between 2000 and 2012. We selected two controls who had been admitted for bronchiolitis just before and just after the index case and 104 of them were treated as inpatients on the ward and 56 were discharged home from the ED. The costs comprised the daily municipal billing for every patient, calculated as the care provider's real costs paid by the municipality that the patient resided in. We calculated the costs for each patient episode, with separate figures for the ED, ward and PICU.

**TABLE 2— Probabilities of PICU Admissions and Effectiveness of High Flow Nasal Cannula (HFNC) Treatment Applied in the Decision Analysis**

| | HFNC group values in the model | Standard low-flow treatment group values in the model |
|---|---|---|
| **Both models 1 and 2** | | |
| Probability of PICU admission | 6.5%,[12] 13%,[13] 5.16%,[14] 4.2%[15] | 6%, 31%[13] |
| Effectiveness | 1.18,[13] 1.0084,[14] 1.018[15] | 1 (settled) |
| **Model 2** | | |
| Probability of NIV | 25%[15] | 18% (unpublished data) |
| Probability of NIV + IV | 2%[15] | 15% (unpublished data) |
| Probability of IV | 1%[15] | 8% (unpublished data) |
| LOS (median in days) | NIV group: 3.75 | NIV group: 5 in PICU + 4 on ward |
| | NIV + IV group: 9.35 | NIV + IV group: 7 in PICU + 0 on ward |
| | IV group: 16.9 | IV group: 9.5 in PICU + 6 on ward |
| | O group: 1.83 | O group: 2 in PICU + 3 on ward |
| | Ward group: 1.83[15] | Ward group: 2 on ward (unpublished data) |
| | LOS similar[13] | |
| **Model 1** | | |
| Cost of hospitalization in both groups (mean) | If PICU admission: €8,061 ($10,975) Only ward admission: €1,834 ($2,497)[11] | |
| **Model 2** | | |
| Costs per day in both groups (mean) | If PICU admission: ED €223 ($304), ward €533 ($726), PICU €961 ($1,308) Only ward admission: ED €232 ($316), ward €556 ($757)[11] | |

PICU, pediatric intensive care unit; ED, emergency department; NIV, non-invasive ventilation; IV, invasive ventilation; O, other reason.
The rate €1 = $1.3615 was used to transfer Euros to US dollars.

Both the total costs of the hospitalization period and the daily costs were accessible. They were presented as Euros and transformed into 2012 levels. Thereafter, the costs were transformed to US dollars and used the rate of €1 = $1.3615.

### Incremental Cost-Effective Ratio ICER

The incremental cost-effective ratio (ICER) describes how much it costs to gain one additional unit of effectiveness and was calculated using the equation

$$ICER = (C_{HFNC} - C_{Standard})/(E_{HFNC} - E_{Standard})$$

where C is the cost and E is the effectiveness.[20]

The results are reported as expected costs and as the ICER.

### Sensitivity Analyses

Because of the uncertainty of the probabilities and the effectiveness, one-, two-, and n-way sensitivity analyses were carried out for both Models 1 and 2. Based on the available literature, the PICU admission rate varied from 4.2% to 13% in the HFNC group[13,15] and from 6% to 31% in the standard treatment group[4,5,13] and these figures were incorporated into the sensitivity analyses. The probabilities of needing ventilatory support were settled as 0.1% to 50%. The effectiveness of HFNC was settled as 1.0–1.2. The costs incorporated into the sensitivity analyses were the median costs, together with the costs at the lower and upper limits of the 95% confidence

interval (95%CI) in our previous study.[11] Likewise, the LOS selected in the sensitivity analyses was the median LOS and the LOS at the lower and upper limits of the 95% CI from the study by Schiblers et al. on HFNC treatment[15] and our unpublished data for standard treatment. The values of the variables used in the sensitivity analyses are presented in Table 3.

### Worst-Case Scenario Analyses

We performed three worst-case scenario analyses (WCSA) for Model 2, with the assumptions of P = 0.0516 and E = 1.0084. In WCSA 1, the upper limits of the 95%CI were applied to both the LOS and the costs in the HFNC treatment branch, and correspondingly, the lower limits of 95%CI for both the LOS and costs in the standard treatment branch.[15,11] In WCSA 2 and 3, the mean costs were applied in both branches, but the LOS that was included was at the upper limit of the 95%CI in the HFNC branch and at the lower limit of the 95%CI in the standard treatment branch. The limits were obtained from Schibler et al.[15] for WCSA 2 and from our own unpublished data for WCSA 3.

### RESULTS

HFNC treatment was cost-effective in Model 1, which included total hospitalization costs and PICU admission probabilities as variables. The expected costs of hospitalization per patient in the HFNC group were €2,153 ($2,932) when the probability of PICU admission (P) was

**TABLE 3— The Values Used in the Sensitivity Analyses**

| | HFNC group values in the model | Standard low-flow treatment group values in the model |
|---|---|---|
| **Both Models 1 and 2** | | |
| Probability of PICU admission | 5–13% | 8–31% |
| Effectiveness | 1.0–1.2 | 0.99–1.01 |
| **Model 2** | | |
| Probability of NIV | 0.1–50% | 0.1–40% |
| Probability of NIV + IV | 0.1–20% | 0.1–30% |
| Probability of IV | 0.1–10% | 0.1–20% |
| LOS | NIV group: 3.0–6.0 | NIV group: 3.26–6.74 in PICU + 1.85–13.38 on ward |
| | NIV + IV group: 6.81–12.81 | NIV + IV group: 5.08–12.02 in PICU + 0–4.95 on ward |
| | IV group: 16.9 | IV group: 1.07–19.59 in PICU + 1.88–9.78 on ward |
| | O group: 1.44–2.75 | O group: 2.3–6.9 in PICU + 2.79–5.87 on ward |
| | Ward group: 1.44–2.75 Similar to standard low-flow treatment group | Ward group: 2–3.5 on ward |
| **Model 1** | | |
| Cost of hospitalization in both groups | If PICU admission: €5,047–9,929 ($6,871–13,518) Only ward admission: €1,568–2,020 ($2,135–2,750)[11] | |
| **Model 2** | | |
| Costs per day in both groups | If PICU admission: ED €212–237 ($289–323) ward €478–565 ($651–769) PICU €739–983 ($1,006–1,338) Only ward admission: ED €218–243 ($297–331) Ward €524–588 ($713–801)[11] | |

PICU, pediatric intensive care; ED, emergency department; NIV, non-invasive ventilation; IV, invasive ventilation; O, other reason.
The rate €1 = $1.3615 was used to transfer Euros to US dollars.

0.0516, the effectiveness (E) was 1.0084, and the costs incorporated into the model were the real mean costs (Fig. 3). The respective costs were higher (€2,208, $3,006) in the standard treatment group. The expected costs at other P and E levels are presented in Table 4, and HFNC treatment remained as cost-effective. When P was 0.0516 and E was 1.0084, the expected HFNC costs varied between €1,748 ($2,379) and €2,428 ($3,306), depending on the cost level which was included—median, lower limit of 95%CI or upper limit of 95%CI. The corresponding figures in the standard treatment group were €1,777–2,495 ($2,419–3,396). HFNC treatment retained dominance in all these sensitivity analyses (data not shown).
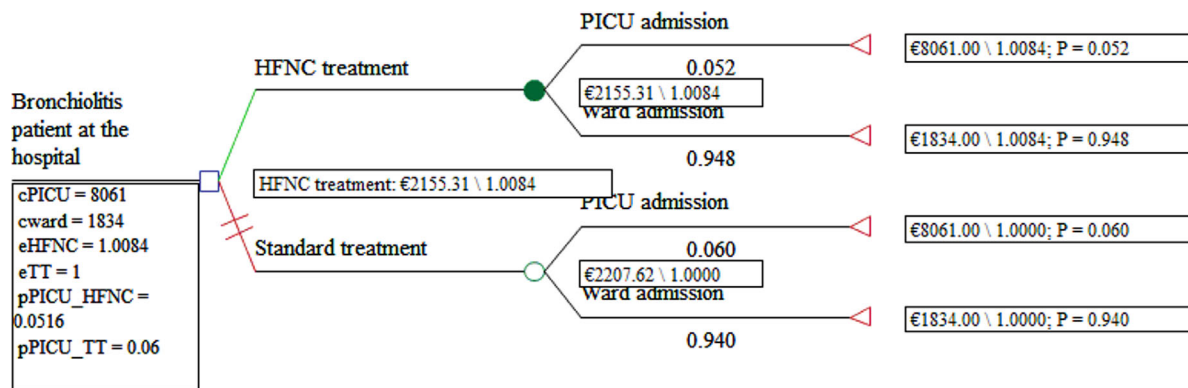


**Fig. 3. The outcome for Model 1. Prefix p indicates probability, c indicates cost (€), and e indicates effectiveness. Costs were expressed as Euros (€) and €1 = $1.3615. PICU, pediatric intensive care unit; HFNC, high-flow nasal cannula treatment; ST, standard treatment.**

TABLE 4— The Expected Costs of HFNC Treatment Versus Standard Treatment in the Two Models, Presented in Relation to the Values Used for Effectiveness (E) and Probabilities (*P*), When the Included Costs Were the Mean Costs

|  | $P = 0.0516, E = 1.0084$ | $P = 0.042, E = 1.018$ | $P = 0.13, E = 1.18$ |
|---|---|---|---|
| Model 1 | €2,153 vs. €2,208 | €2,096 vs. €2,208 | €2,644 vs. €3,764 |
|  | $2,932 vs. $3,006 | $2,853 vs. $3,006 | $3,600 vs. $5,125 |
| Model 2 | €1,326 vs. €1,598 | €1,312 vs. €1,598 | €1,442 vs. €2,654 |
|  | $1,805 vs. $2,175 | $1,786 vs. $2,175 | $1,963 vs. $3,601 |

*P*, probability of PICU admission in HFNC treatment; E, effectiveness of HFNC treatment.
The rate €1 = $1.3615 was used to transfer Euros to US dollars.

The ICER was €65 ($88), when *P* was 0.0516, E was 1.0084 and the costs were the mean hospitalization costs. This means that one percent reduction in the PICU admission rate due to HFNC treatment resulted saving of €65 ($88) for every treatment episode. The effectiveness of 1.0084 means, however, a 0.84% reduction in the PICU admission rates. When we examined the other cost levels—median, upper or lower limit of the 95%CI—we found that the ICER varied from €35 ($48) to €80 ($109). HFNC treatment retained dominance in all these sensitivity analyses (data not shown).

HFNC treatment was also cost-effective in Model 2, which comprised the mean costs per day multiplied by the LOS, the probabilities of PICU admission, and the probabilities of the need of different ventilatory supports. The expected costs of hospitalization per patient in the HFNC group were €1,326 ($1,805), when *P* was 0.0516 and E was 1.0084, and the costs incorporated into the model were the real mean costs (Fig. 4), compared with €1,598 ($2,175) for the standard treatment. The expected costs at other *P* and E levels are presented in Table 4, and HFNC treatment remained as cost-effective. When *P* was 0.0516 and E was 1.0084, the expected costs in the HFNC group varied from €1,230 to 1,396 ($1,675 to 1,900), depending on whether the mean, median, or lower or upper level of the 95%CI was used. The corresponding
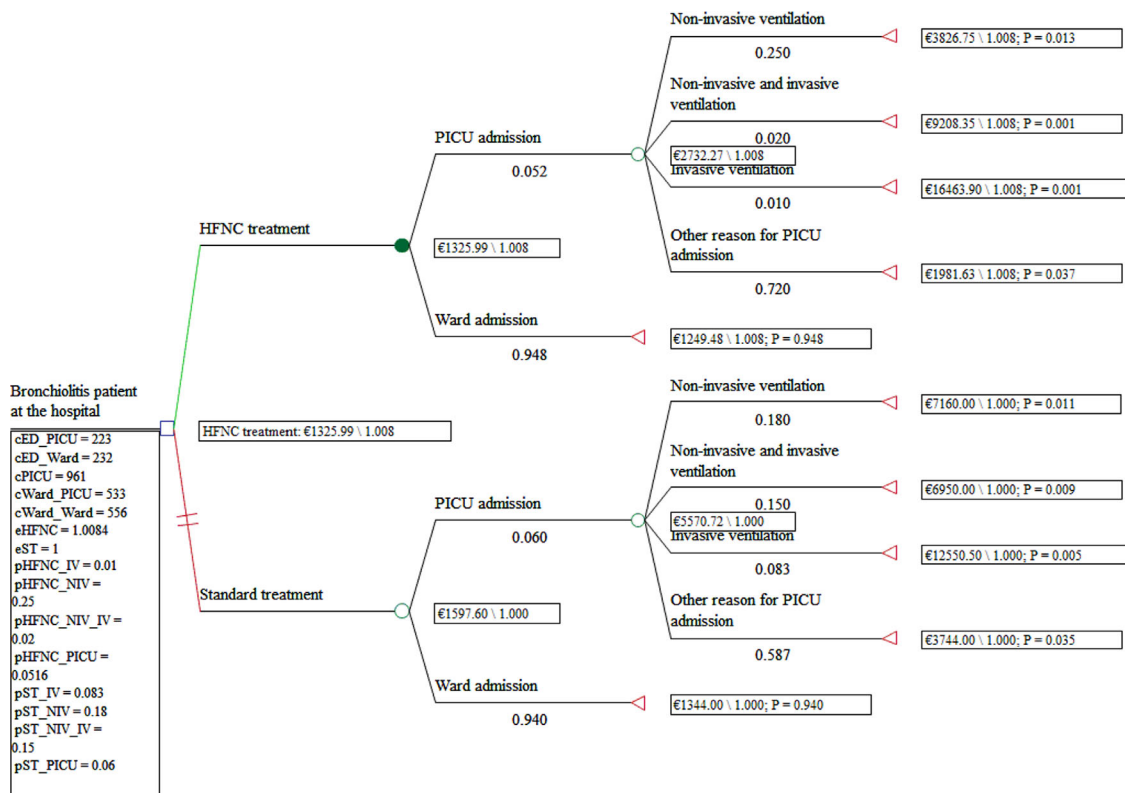


Fig. 4. The outcome for Model 2. Prefix p indicates probability, c indicates cost (€), and e indicates effectiveness. Costs were expressed as Euros (€) and €1 = $1.3615. PICU, pediatric intensive care unit; ED, emergency department; HFNC, high-flow nasal cannula treatment, ST, standard treatment; NIV, non-invasive ventilation; IV, invasive ventilation.

figures in the standard treatment group were €1,465–1,680 ($1,995–2,287). HFNC retained dominance in all these sensitivity analyses (data not shown).

The ICER values in the Model 2 were higher compared to Model 1. When $P$ was 0.0516, E was 1.0084 and the costs were the mean hospitalization costs, the ICER was €324 ($441). This means that 1% reduction in the PICU admission rate due to HFNC treatment resulted saving of €324 ($441) for every treatment episode. When we examined the other cost levels—median, upper or lower limit of the 95%CI—we found that the ICER varied from €280 ($381) to €338 ($460).

In contrast, HFNC lost dominance in the three WCSAs. When the LOS and costs were at the upper limit of the 95%CI in the HFNC treatment group and at the lower limit of the 95%CI in the standard treatment group, the expected costs were €1,788 ($2,434) for HFNC versus €1,704 ($2,320) for standard treatment (WCSA 1). When the LOS was at the upper limit of the 95%CI in the HFNC treatment group, and at the lower limit of the 95%CI in the standard treatment group, and the included costs were the mean costs for both groups, the expected costs for HFNC treatment were €1,875 ($2,553) versus €1,204 ($1,639) for standard treatment in WCSA 2 and €2,524 ($3,436) versus €1,790 ($2,437) in WCSA 3.

## DISCUSSION

The main result of this study was that HFNC was cost-effective compared to standard treatment in infants with bronchiolitis who need additional oxygen. Consequently, HFNC should be considered for every bronchiolitis patient who needs oxygen support. In this study, the cost-effectiveness of HFNC mainly came from the reduction of the need for PICU admissions.

HFNC treatment can be carried out on a pediatric ward without the need for PICU facilities.[12,13,16,22] Our estimates of how much HFNC treatment can reduce PICU admissions was based on retrospective studies using historical controls, and we assumed that the PICU admission rates would reduce as much as the HFNC treatment reduced intubation rates in these studies, that is, 14%[14] to 30%.[15] However, data based on historical controls are not very reliable. The reduction in the need for intensive care was 18% in the only prospective study,[13] but in that study, the PICU admission rate was surprisingly high, 31%, in the retrospectively collected control group treated with low-flow oxygen support at the same time.

We monitored the variability and uncertainty of the available data by doing sensitivity analyses, and HFNC retained dominance, even with the lowest included effectiveness levels. Such dominance was lost only in the worst-case scenarios, which are extremely rare, but of course, may sometimes come true.

The costs of the present study were from one center with lower PICU admission rates than included in the model. In two recent Finnish studies,[4,5] the annual PICU admission rate was 6% in infants who were hospitalized for bronchiolitis, and our hospital participated in one of them.[4] Thus, the cost-effectiveness observed in the sensitivity analyses made at low effectiveness levels, still favoring HFNC over standard oxygen support, reflects the situation in our hospital. The model we used provides a method to calculate the costs at different effectiveness levels in other hospitals, by replacing the applied costs with the actual expenses of those hospitals.

HFNC treatment offers many beneficial physiologic effects in infant bronchiolitis, but only observational studies with small numbers of patients are available. When high 8 and low 2 L/min flow rates were compared in 13 infants, respiratory rates decreased, oxygen saturation increased and less supplementary oxygen was needed with the 8 L/min flow rate.[17] Nasopharyngeal pressure increased linearly with flow rates up to 6 L/min in 25 infants and, at this level, bronchiolitis severity scores improved significantly.[23] Work of breathing decreased after starting HFNC treatment in 21[18] and 14[19] infants with bronchiolitis. When 27 infants were treated with HFNC for 48 hr, a significant increase in oxygen saturation and a significant decrease in respiratory rate were observed.[16] The only randomized controlled study in 19 infants found that the median oxygen saturation was higher in the HFNC group than in the standard oxygen support group during the first 12 hr.[24] In a retrospective study of 34 infants, HFNC treatment was equally effective as nCPAP treatment when assessed by different physiological measurements.[25]

HFNC treatment has been reported to be well tolerated[12,16,22,24] and easy to use on a pediatric ward.[13,16,24] A prospective observational study of 27 infants on a pediatric ward did not report any unexpected interruptions, complications, PICU transfers or the need for other respiratory supports.[16] Therefore, all our analyses were based on the presumption that HFNC treatment can be provided on the pediatric ward. If the child is, however, admitted to the PICU, HFNC treatment is still cost-effective if it shortens the PICU stay. Even if the PICU stay is not shortened, HFNC treatment could still be cost-effective, based on the less need of ventilatory support using other methods.

Our results were based on the assumption that HFNC is used instead of standard low-flow oxygen therapy in all bronchiolitis cases in which additional oxygen is needed. On the other hand, there are no research-based cut-off limits for beginning or weaning of oxygen support for infants with bronchiolitis. In the international guidelines, the limits for beginning of oxygen administration have been rather similar, that is oxygen saturation persistently less than 90% to less than 92%.[26] Two of the four here

cited HFNC studies reported the oxygen saturation levels used as indications of HFNC treatment, and they were 92%[15] and 94%[13] when the patient was on low-flow oxygen support. In a British study on 68 infants with bronchiolitis, ending oxygen administration for recovering bronchiolitis at stable 90% saturation rather than at stable 94% saturation resulted in a discharge from hospital on average 22 hr earlier.[27] Thus, accepting lower oxygen saturations can significantly reduce the use and shorten the length of oxygen administration reducing further the costs, but the clinical and safety issues need further studies.

Our hospital provides inpatient care to a population of approximate 6,000 infants of less than 12-months old. In 2000–2012, 80 infants—a mean of 6.2 per year—were treated in the PICU.[11] Theoretically, providing HFNC treatment when oxygen administration is needed in infant bronchiolitis, would reduce annual total hospitalization costs €16,320–48,960 ($22,220–66,659) in our hospital. These estimates were based on average computational total hospitalization cost at the PICU admission probability of 0.0516 and HFNC effectiveness of 1.0084. As RSV infections occur as short and intensive epidemics, and the best cost-effectiveness is reached if HFNC is always given when oxygen is required, the number of HFNC devices may be the limiting factor at the peak of epidemics. The approximate purchase price of one HFNC device is €4,900 ($6,671), which means that the annual savings cover the acquisition of three to ten devices.

In the two reviews on HFNC treatment in infant bronchiolitis the authors concluded that the evidence for or against is still lacking due to the shortage of high-quality randomized controlled trials. The Cochrane review on HFNC therapy for infant bronchiolitis, published in 2014, accepted only one randomized controlled trial.[28] As discussed above, that pilot study included 19 infants and confirmed higher oxygen saturation for 12 hr, when HFNC was compared to head-box oxygen support.[24] A later review published in 2015 accepted one randomized controlled trial more.[29] That study on 75 infants with bronchiolitis did not report any differences in clinical scores between those treated with HFNC (plus epinephrine) and those treated with hypertonic saline (plus epinephrine).[30] These studies were not aimed, and so, were underpowered for more hard outcomes like PICU admission rate or length of hospital stay.

In conclusion, our theoretical analysis showed that treating all infants, who need oxygen support during hospitalization for bronchiolitis, with the HFNC method instead of standard low-flow treatment is cost-effective. The estimated reductions in the need for intensive care were based on retrospective studies that used historical controls. Therefore, prospective randomized controlled trials are urgently needed to provide evidence of the indications, benefits and cost-effectiveness of using high-flow oxygen therapy for infants with bronchiolitis.

## ACKNOWLEDGMENT

## REFERENCES

1. Hasegawa K, Tsugawa Y, Brown D, Mansbach JM, Camargo CA Jr. Trends in bronchiolitis hospitalizations in the United States, 2000–2009. Pediatrics 2013;132:28–36.
2. Leader S, Kohlhase K. Recent trends in severe respiratory syncytial virus (RSV) among US Infants, 1997 to 2000. J Pediatr 2003;143:S127–S132.
3. Smyth R, Openshaw P. Bronchiolitis. Lancet 2006;68:312–322.
4. Jartti T, Aakula M, Mansbach JM, Piedra PA, Bergroth E, Koponen P, Kivistö JE, Sullivan AF, Espinola JA, Remes S, et al. Hospital length-of-stay is associated with rhinovirus etiology of bronchiolitis. Pediatr Infect Dis J 2014;33:829–834.
5. Pruikkonen H, Uhari M, Dunder T, Pokka T, Renko M. Infants under 6 months with bronchiolitis are most likely to need major medical interventions in the 5 days after onset. Acta Pediatr 2014;103:1089–1093.
6. Hervás D, Reina J, Yañez A, del Valle JM, Figuerole J, Hervás JA. Epidemiology of hospitalization for acute bronchiolitis in childer: differences between RSV and non-RSV bronchiolitis. Eur J Clin Microbiol Infect Dis 2012;31:1975–1981.
7. Mansbach JM, Piedra PA, Stevenson MD, Sullivan AF, Forgey TF, Clark S, Espinola JA. Camargo CA Jr; MARC-30 Investigators. Prospective multicenter study of children with bronchiolitis requiring mechanical ventilation. Pediatrics 2012;130:e492–e500.
8. AAP, American Academy of Pediatrics, Diagnosis and management of bronchiolitis. Pediatrics 2006;118:1774–1793.
9. Schroeder A, Mansbach J. Recent evidence on the management of bronchiolitis. Curr Opin Pediatr 2014;26:328–333.
10. Øymar K, Skjerven H, Mikaelsen I. Acute bronchiolitis in infants, a review. Scand J Trauma Resusc Emerg Med 2014;22:23–33.
11. Heikkilä P, Forma L, Korppi M. Hospitalisation costs for infant bronchiolitis are up to 20 times higher if intensive care is needed. Acta Paediatr 2015;104:269–273.
12. Kelly G, Simon H, Sturm J. High-flow nasal cannula use in children with respiratory distress in the emergency department. Predicting the need for subsequent intubation. Pediatr Emerg Care 2013;29:888–892.
13. Mayfield S, Bogossian F, ÓMalley L, Schibler A. High-flow nasal cannula oxygen therapy for infants with bronchiolitis: pilot study. J. Paediatr Child Health 2014;50:373–378.
14. McKiernan C, Chua LC, Visintainer PF, Allen H. High-flow nasal cannulae therapy in infants with bronchiolitis. J Pediatr 2010; 156:634–638.
15. Schibler A, Pham TM, Dunster KR, Foster K, Barlow A, Gibboms K, Hough JL. Reduced intubation rates for infants after introduction of high-flow nasal prong oxygen delivery. Intensive Care Med 2011;37:847–852.
16. Bressan S, Balzani M, Krauss B, Pettenazzo A, Zanconato S, Baraldi E. High-flow nasal cannula oxygen for bronchiolitis in a pediatric ward: a pilot study. Eur J Pediatr 2013;172:1649–1656.
17. Hough J, Pham T, Schibler A. Physiologic effect of high-flow nasal cannula in infants with bronchiolitis. Pediatr Crit Care Med 2014;15:e214–e219.
18. Milési C, Baleine J, Matecki S, Durand S, Combes C, Novais AR, Cambonie G. Is treatment with high flow nasal cannula effective in

acute viral bronchiolitis? A physiologic study. Intensive Care Med 2013;39:1088–1094.

19. Pham T, ÓMalley L, Mayfield S, Martin S, Schibler A. The effect of high-flow nasal cannula therapy on the work of breathing in infants with bronchiolitis. Pediatr Pulmonol 2015;50:713–720.

20. Morris S, Devlin N, Parkin D. Economic analysis in health care, 2nd edition. Glasgow: John Wiley & Sons Ltd; 2009.

21. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation. New York: Oxford University Press; 2006.

22. Spentzas T, Minarik M, Patters AB, Vinson B, Stidham G. Children with respiratory distress treated with high-flow nasal cannula. J Intensive Care Med 2009;24:323–328.

23. Arora B, Mahajan P, Zidan MA, Sethuraman U. Nasopharyngeal airway pressures in bronchiolitis patients treated with high-flow nasal cannula oxygen therapy. Pediatr Emerg Care 2012;28:1179–1184.

24. Hilliard TN, Archer N, Laura H, Heraghty J, Cottis H, Mills K, Ball S, Davis P. Pilot study of vapotherm oxygen delivery in moderately severe bronchiolitis. Arch Dis Child 2012; 97:182–183.

25. Metge P, Grimaldi C, Hassid S, Thomachot L, Loundou A, Martin C, Michel F. Comparison of a high-flow humified nasal cannula to nasal continuous positive airway pressure in children with acute bronchiolitis: experience in a pediatric intensive care unit. Eur J Pediatr 2014;173:953–958.

26. Zorc JJ, Hall CB. Bronchiolitis: recent evidence on diagnosis and management. Pediatrics 2010;125:342–349.

27. Cunningham S, McMurray A. Observational study of two oxygen saturation targets for discharge in bronchiolitis. Arch Dis Child 2012;97:361–363.

28. Beggs S, Wong ZH, Kaul S, Ogden KJ, Walters JA. High-flow nasal cannula therapy for infants with bronchiolitis. Cochrane Database Syst Rev. 2014;1:CD009609. DOI: 10.1002/14651858. CD009609.pub2

29. Sinha IP, McBride AK, Smith R, Fernandes RM. CPAP and high-flow nasal cannula oxygen in bronchiolitis. Chest 2015;148:810–823.

30. Bueno Campaña M, Olivares Ortiz J, Notario Muñoz C, Rupérez Lucas M, Fernández Rincón A, Patiño Hernández O, Calvo Rey C. High flow therapy versus hypertonic saline in bronchiolitis: randomised controlled trial. Arch Dis Child 2014;99:511–515.

## Erratum

In the article:

High-flow oxygen therapy is more cost-effective for bronchiolitis than standard treatment − A decision-tree analysis. Heikkilä P, Forma L, Korppi M. Pediatr Pulmonol. 2016 Dec;51(12):1393–1402. doi: 10.1002/ppul.23467.

All the incremental cost-effectiveness ratio (ICER) values were erroneously expressed as positive although they all were negative. The deductions were written correctly; negative ICER values mean savings.

.