Continuous Negative Extrathoracic Pressure and Bronchiolitis

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Abstract

Bronchiolitis is the commonest cause of acute respiratory failure in infancy and several hundred children need respiratory support for the condition each year in the United Kingdom. Continuous negative extrathoracic pressure (CNEP) has been used to support such children but concerns about its possible association with significant harm prompted a government enquiry into the conduct of research at a UK centre using the technique. This retrospective study was designed to address these concerns by careful evaluation of outcome in two matched cohorts. Fifty children who had received CNEP for bronchiolitis as infants were compared with 50 controls who were treated in another hospital during the same period. Pre-treatment variables, demographics and neonatal factors were well matched in the two groups. In all subjects questionnaires and clinical examination were used to assess respiratory symptoms, disability and health-related quality of life whilst respiratory function was assessed by measuring airway resistance using the interrupter technique (*R*int), by spirometry and by bronchodilator responsiveness. CNEP was associated with reduced need for, and shorter duration of, positive pressure ventilation but with longer periods in oxygen and hospital. Median *R*int was 16.5% higher in the CNEP cohort ($p<0.001$) and median FEF_{25-75} was 9.3% lower ($p=0.029$). There were no significant differences between the groups in FEV_1, FVC, bronchodilator responses or respiratory symptoms, or in the prevalence of moderate or severe disability

(Mantel-Haenszel statistic 1.40, 95% confidence intervals: 0.64 -3.04, p=0.39). Median health utility indices were similar; CNEP 1.00 (interquartile range: 0.85-1.00), controls 0.99 (interquartile range: 0.81 - 1.00), n=48 pairs, p= 0.37. The higher *R*int and lower FEF_{25-75} in the CNEP group represent a small difference in respiratory function that may be attributable to population differences but a CNEP effect cannot be excluded. Further evaluation of the use of CNEP in bronchiolitis requires a prospective, controlled study.

Declaration

I declare that this thesis is my own work except where acknowledged and is based on research that was undertaken by me in the Department of Child Health, School of Human Development, University of Nottingham between August 2002 and August 2004.

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1 Literature Review

1.1 Introduction

Bronchiolitis is the commonest lower respiratory tract infection in infancy and the most frequent cause of acute respiratory failure in children admitted to paediatric intensive care units in the UK and North America (PICANet National Report, 2006, Randolph et al., 2003). About 2% of children admitted with bronchiolitis require ventilatory support (Behrendt et al., 1998). Babies with pre-existing lung disease, such as infants born preterm who develop chronic lung disease or infants with congenital heart disease, are more likely to require respiratory support with a bronchiolitis illness - ventilation rates as high as 17% in infants with chronic lung disease and 18.8% in infants with congenital heart disease have been reported (Navas et al., 1992). Respiratory support is provided in most cases by positive pressure ventilation (PPV) (Lebel et al., 1989, Outwater and Crone, 1984) which requires intubated subjects to be sedated and can lead to complications including injury to the airway or lungs (Orlowski et al., 1980). The complications of mechanical ventilation have prompted a number of investigators to explore less-invasive methods of respiratory support. Nasal continuous positive airway pressure (CPAP) has been used successfully since the early 1970s to manage children with bronchiolitis-associated respiratory failure (Beasley and Jones, 1981, Soong et al., 1993). Continuous negative extrathoracic pressure (CNEP) has also been used following improvements in the 1980s in the delivery of this mode of respiratory support (Samuels and Southall,

1989). In some cases intermittent negative extrathoracic pressure (INEP) has been used in addition to CNEP thus providing a further level of respiratory support, i.e. negative pressure ventilation (Al-balkhi et al., 2005). Neither CPAP nor CNEP has been assessed in a randomised trial.

Samuels and Southall (1989) were the first to report the use of CNEP in children with bronchiolitis in an uncontrolled trial of 88 infants with respiratory failure due to a variety of disorders, including 7 with 'asthma or bronchiolitis'. When used as an adjunct to positive pressure ventilation, CNEP was associated with a 15% mean reduction in oxygenation after 2 hours in the group as a whole, without significant complications. However, the small number of infants with bronchiolitis and the lack of a control group limit the significance of these findings.

An abstract report by Hartmann et al. (1994b) describes the findings of a randomised controlled pilot study of the use of CNEP for bronchiolitis in 15 subjects and 18 controls. Infants with bronchiolitis were recruited if they required an inspired oxygen fraction ≥ 0.4 to maintain saturations between 96-99%. CNEP was associated with a reduction in FiO_2 to ≤ 0.3 within 1 hour in 4 subjects compared to none of the controls. One child in the control group and none in the CNEP group subsequently required positive pressure ventilation.

Negative pressure ventilation (NPV) was used routinely at the North Staffordshire Hospital (NSH) from 1993-1999, for the management of infants with bronchiolitis-associated respiratory failure. A retrospective cohort study of 52 infants with bronchiolitis-related apnoea, 31 of whom were treated at NSH (a CNEP centre) and 21 who were treated at the Queen's Medical Centre (QMC), a centre which did not use NPV, suggested that its use was associated with a reduced rate of intubation and a shorter PICU stay (Al-balkhi et al., 2005).

The safety of CNEP was questioned following a trial in which 244 premature babies were randomly assigned to receive conventional respiratory support (standard group) or a combination of CNEP and conventional respiratory support (CNEP group) for the treatment of respiratory distress syndrome (Samuels et al., 1996). There were 28 deaths in the CNEP group and 22 deaths in the standard group. Cranial ultrasound abnormalities were identified in 15 babies in the CNEP group and in 10 babies in the standard group. Neither outcome measure was significantly different between the groups, however the findings led to public concern that CNEP use might result in a higher rate of later neurodisability. These concerns were extended to the use of CNEP in bronchiolitis. A government enquiry was commissioned to investigate these and other apprehensions about the conduct of the research. One of the outcomes of the enquiry was a recommendation that "---a substantial audit of the use of CNEP at NSH be carried out to

see if claims of significant benefit or damage can be substantiated" (Griffiths, 2003).

No previous studies have reported long-term outcome following the use of this technique for bronchiolitis. This thesis reports the findings of a matched cohort study of children treated with CNEP for bronchiolitis, which was designed in response to this report. The study aim was to evaluate the previous clinical experience of the treatment of bronchiolitis with CNEP, with the public concerns in mind, so as to identify any long-term respiratory or neurological consequences of its use. By way of background to the study, the literature relating to short and long-term outcome following bronchiolitis has been reviewed. The published data on short-term outcome following the use of CNEP for bronchiolitis is evaluated and results from studies reporting the use of CNEP in children with other relevant conditions is discussed. A number of the studies evaluated included children where both *intermittent* (INEP) and *continuous* negative pressure support (CNEP) were provided. These children have been referred to as receiving negative pressure ventilation (NPV) in the review that follows. Areas of research where data are lacking have been highlighted.

1.2 Acute bronchiolitis

1.2.1 Incidence and aetiology

Bronchiolitis is the most common lower respiratory tract infection in infants admitted to hospital. It is estimated that 100,000 cases are admitted annually in the United States (Shay et al., 1999). In the United Kingdom, respiratory syncytial virus (RSV) bronchiolitis is reported to account for about 20,000 hospital admissions annually, which is approximately 3% of the birth cohort (Handforth et al., 2000). RSV is the commonest aetiological agent in the clinical syndrome of bronchiolitis and accounts for 50-90% of all admitted cases (Hall, 1998). New techniques of virus isolation such as reverse transcription polymerase chain reaction (RT-PCR) are helping to identify the role of other viruses in acute bronchiolitis and its subsequent long-term outcome. Human Metapneumovirus (hMPV), identified as a significant respiratory pathogen in 2001, causes a similar spectrum of illness to RSV and may be the second most common cause of bronchiolitis (van den Hoogen et al., 2001, Foulongne et al., 2006). It has become evident that hMPV co-infection with RSV is the cause of particularly severe bronchiolitis in some cases (Williams et al., 2004, Foulongne et al., 2006). Similar virus isolation techniques have identified rhinovirus as a frequent cause of bronchiolitis in an older age group than that typically affected by RSV. Rhinovirus bronchiolitis is also more frequently associated with subsequent wheezing than is RSV bronchiolitis (Kotaniemi-Syrjanen et al., 2003). Other aetiological agents known to cause bronchiolitis include adenovirus, influenza,

parainfluenza, coronavirus, enterovirus and human bocavirus discovered in 2005 (Jartti et al., 2005, Allander et al., 2005). In addition *Mycoplasma pneumoniae* is occasionally associated with a wheezing illness in infants.

1.2.2 Clinical features

Bronchiolitis is a clinical diagnosis. In the United Kingdom the term describes an illness in infants that begins as an upper respiratory tract infection (URTI) followed by signs of respiratory distress, a harsh cough, bilateral crepitations, air trapping and wheezing (Gardner, 1968). In the United States and some European countries, the diagnosis of bronchiolitis may include children up to 2 years of age with an acute wheezing illness who have a history of recurrent bouts of wheezing. In the UK such children would be diagnosed as having viral induced wheeze rather than bronchiolitis. The differences in definition are important when evaluating the results of therapeutic interventions in clinical trials and when comparing data about incidence, morbidity, mortality and long-term outcomes between studies. Most children with bronchiolitis have a self-limiting illness and are managed conservatively at home. Infants with moderate or severe bronchiolitis who have marked difficulty breathing with hypoxia require hospital admission. Mortality in infants who are otherwise healthy is about 0.5% (Behrendt et al., 1998) but is higher (~3.5%) in children with underlying conditions such as cardiac or chronic lung disease (Navas et al., 1992). Other

groups at ‘high-risk’ of severe disease are preterm infants and children with congenital or acquired immunodeficiency (Stretton et al., 1992) as well as children with cystic fibrosis.

A subgroup of children requiring ventilation for RSV infection traditionally presumed to have bronchiolitis have recently been identified as having a different pattern of illness characterised by the radiological appearances of diffuse consolidation without hyperinflation as opposed to the classical appearance of gross hyperinflation without consolidation. The pattern of illness is more accurately described as RSV pneumonia and these children generally fulfil the clinical criteria of Acute Respiratory Distress Syndrome (ARDS). The distinction between the different clinical entities is important because the response to treatment and outcome may well be different for the 2 groups. One obvious difference is the prolonged length of ventilation in the group with pneumonia compared to those with bronchiolitis (Tasker et al., 2000).

1.2.3 Pathophysiology

The pathological changes found in bronchiolitis were first described in autopsy specimens from infants dying of the condition and are presumed to be similar in those with a milder form of the illness who survive (Aherne et al., 1970). The observed post mortem changes are

those of acute inflammatory obstruction in the small airways. The virus colonises the respiratory tract epithelium and replicates causing epithelial necrosis and destruction of the cilia. The epithelial cell destruction triggers an inflammatory response with cellular infiltrate (predominantly lymphocytes) and oedema of the submucosa. There is also increased secretion of mucus from goblet cells, which combines with desquamated epithelial cells to form thick mucus plugs. The mucus plugs cause obstruction of the bronchioles, which results in both air trapping and lobular collapse to varying degrees. This leads to ventilation perfusion mismatch resulting in hypoxaemia (Aherne et al., 1970, Hall, 1998).

1.2.4 Preventative therapies

1.2.4.1 Vaccine

There is currently no vaccine available to prevent RSV infection, which is responsible for up to 90% of admissions with bronchiolitis. The first trials of a formalin-inactivated RSV vaccine in the 1960's induced a good IgG response in healthy volunteers but when assessed in clinical trials, the severity of subsequent infection was increased rather than decreased in those who had been immunised (Kapikian et al., 1969, Kim et al., 1969). Problems to be surmounted in the development of a vaccine include the need to induce immunity to multiple strains of the virus. A series of boosters would be required for a vaccine to be

effective because natural infection with RSV does not prevent re-infection.

1.2.4.2 Immunoprophylaxis:

The most significant progress in the management of bronchiolitis in recent years has been in the development of agents giving passive immunisation against RSV. Two products are currently available for use as immunoprophylaxis in infants at high-risk of developing severe RSV bronchiolitis. The first to become available was intravenous RSV immunoglobulin (RSV-IG). The prophylactic administration of RSV-IG to high-risk infants and young children was evaluated in a prospective, multicentre, blinded, randomised controlled trial involving 249 children (Groothuis et al., 1993). Subjects were randomly assigned to treatment groups, which received high dose (750mg/kg) or low dose (150mg /kg) monthly infusions of RSV-IG, or to a control group that received no infusions. The investigators reported significantly fewer lower respiratory tract infections (7 versus 20 in the controls; p=0.01) and hospitalisations (6 versus 18 in the controls; p=0.02) and in addition reduced days in intensive care (1 versus 34; p=0.05) in children treated with high dose RSV-IG when compared with controls. Subjects in the low dose group were reported to have a significant reduction only in the number of days in intensive care (0 versus 34; p=0.03). Disadvantages of RSV-IG include the need for intravenous administration of a large volume (15ml/kg) with its potential for fluid overload, a long duration of

administration (2- 4hrs) and expense. The study found an increased incidence of adverse events in infants with cyanotic congenital heart disease and so RSV-IG is not recommended for this high-risk group.

Another form of passive immunisation uses a humanised monoclonal antibody (Palivizumab). In a randomised, double blind, multi-centre trial (IMpact-RSV Trial), monthly palivizumab prophylaxis or placebo was administered to 1502 children by intramuscular injection over the 5 months of the RSV season (The IMpact-RSV Study Group, 1998). Palivizumab use was associated with a 55% reduction in RSV-related hospitalisation (95% confidence intervals 38% -72%), fewer days in hospital (62.6 days/ 100 children- placebo group, 36.4 days/ 100 children- Palivizumab group) and a lower incidence of intensive care admission (3% -placebo group and 1.3% in Palivizumab group, p=0.026). The effect of Palivizumab remained evident in subgroups of infants with bronchopulmonary dysplasia and haemodynamically significant congenital heart disease (Feltes et al., 2003). The main advantages of palivizumab over RSV-IG are its relative ease of administration and lack of interference with normal immunisations; its main disadvantage is its high cost. The benefits of palivizumab over RSV-IG have been assessed to outweigh any disadvantages by most clinicians and as a result it is preferred (Kimpen, 2002). A recent study of the healthcare utilisation of 190 prematurely born children with chronic lung disease found significantly increased respiratory morbidity and health service cost following RSV infection (Greenough et al.,

2004). In light of these data, the UK Department of Health advisory body on immunisations, the Joint Committee on Vaccination and Immunisation (JCVI), has revised its recommendations for the use of palivizumab prophylaxis (Joint Committee on Vaccination and Immunisation, 2005) - it was previously recommended only for children with chronic lung disease (CLD) who also required home oxygen but is now recommended for *all* children with CLD, even those not needing home oxygen. The groups recommended to receive palivizumab by the JCVI are:

1. Children under 2 years of age with chronic lung disease who have required supplementary oxygen for at least 28 days from birth or who are receiving home oxygen.

2. Infants less than 6 months of age who have a left to right shunt, haemodynamically significant congenital heart disease and/or pulmonary hypertension.

3. Children under 2 years of age with severe congenital immunodeficiency.

1.2.5 Treatment

Children with bronchiolitis require hospital admission if they are hypoxic or are unable to maintain adequate hydration; those in high-risk groups may require admission at an earlier stage of illness than otherwise healthy children. Supportive care with oxygen and nasogastric feeding

(if fluid intake is inadequate) are the mainstays of treatment for children with mild or moderate bronchiolitis. Results from numerous studies on a range of other treatment options have been disappointing with inconsistent findings or no evidence of benefit. Despite the prominent role that inflammation plays in the pathogenesis of airway obstruction, a systematic review of randomised controlled trials of systemic corticosteroids in acute bronchiolitis found no benefit in terms of length of hospital stay or of clinical scores (Patel et al., 2004). The lack of benefit from corticosteroids has recently been confirmed in a multi-centre randomised controlled trial, which compared a single dose of oral dexamethasone with placebo in 600 children diagnosed with bronchiolitis in the A&E department. No significant difference was found in the rates of hospital admission, respiratory status after 4 hours or later outcomes such as length of hospital stay, later medical consultations or admissions (Corneli et al., 2007).

Evidence relating to the use of bronchodilators in bronchiolitis is inconclusive; most studies suggest they have no benefit and might be deleterious whilst a few studies have found some clinical improvement (Schuh et al., 1990, Wang et al., 1992, Ho et al., 1991, Dobson et al., 1998, Klassen et al., 1991). A systematic review of randomised controlled trials comparing bronchodilators with placebo in bronchiolitis concluded that bronchodilators produce a modest short-term improvement in clinical scores but no reduction in the rate or duration

of hospitalisation (Kellner et al., 2000) - however, the definition of bronchiolitis used in some of the trials allowed inclusion of children with recurrent wheeze which will have biased the results in favour of bronchodilators.

Ribavarin is currently the only licensed antiviral agent for use in RSV-bronchiolitis but its use seems to bring limited clinical benefit. A prospective, double blind multi-centre study (Groothuis et al., 1990) was undertaken to assess the efficacy of early ribavarin intervention in mild RSV illness compared with placebo. Forty seven children with bronchopulmonary dysplasia or congenital heart disease were enrolled. Early administration of ribavarin (<72hrs after onset of symptoms) was associated with improved oxygenation and clinical scores in 20 infants compared with 27 controls. In a later prospective controlled study, the Pediatric Investigators Collaborative Network on Infections in Canada conducted a subset analysis of 750 children with RSV lower respiratory tract infection enrolled in the 1993-1994 RSV database (Law et al., 1997). They observed no significant benefit of ribavarin therapy in premature infants, infants with congenital heart disease or chronic lung disease with respect to a range of outcome measures including hospitalisation, duration of ventilation, stay in intensive care, and mortality. A Cochrane review of randomised trials comparing ribavarin with placebo in infants with RSV lower respiratory tract infection found that ribavarin may reduce duration of mechanical ventilation and days

of hospitalisation but concluded that it has not been shown to significantly reduce respiratory deterioration (treatment failure defined by pre-specified criteria leading to withdrawal from the study) or mortality (Ventre and Randolph, 2007). Trials of ribavarin have generally been inadequately powered to determine the outcome measures reliably. Ribavarin is currently only recommended for use in immunocompromised patients to reduce the duration of viral shedding (Kneyber et al., 2000).

1.2.6 Management of respiratory failure

Infants with bronchiolitis may need respiratory support for either recurrent apnoea or increased work of breathing with respiratory failure. Depending on which denominator is used the estimated proportions needing respiratory support vary between 2% and 9%. Two large, retrospective, population-based studies have estimated that about 2% of all infants admitted with bronchiolitis require ventilatory support (Shay et al., 1999, Behrendt et al., 1998) but larger proportions (7-9%) have been reported in hospital-based studies which tend to be from tertiary centres with a referral bias (Wang et al., 1995, Outwater and Crone, 1984). The population-based studies provide a more accurate assessment of the frequency with which respiratory support is required, whereas the hospital-based rates may be of more relevance to tertiary centres, which are seeking to plan service provision.

Several modes of respiratory support have been used in the management of bronchiolitis-associated respiratory failure. Intermittent positive pressure ventilation (Downes and Striker, 1966, Lebel et al., 1989, Outwater and Crone, 1984), continuous positive airway pressure (Beasley and Jones, 1981, Soong et al., 1993), negative extrathoracic pressure (Samuels and Southall, 1989, Al-balkhi et al., 2005), high frequency oscillation ventilation (Duval et al., 1999) and extracorporeal membrane oxygenation (Flamant et al., 2005) have all been used successfully - but none in the context of a randomised controlled trial. A helium/oxygen mixture (Heliox) has been used in infants with bronchiolitis-related respiratory failure to observe if it might improve clinical scores or reduce the need for mechanical ventilation (Cambonie et al., 2006, Liet et al., 2005, Hollman et al., 1998). A prospective, randomised, double-blind study of 20 infants with moderate to severe bronchiolitis found a significant difference in the modified 'Wood clinical asthma score' after 1 hour of heliox use (Cambonie et al., 2006). However, a multi-centre, randomised, double-blind placebo controlled study of 39 infants with severe bronchiolitis, found no difference in the need for intubation between subjects and controls following the use of heliox for at least 24 hours (Liet et al., 2005). Exogenous surfactant is another adjunct that has been investigated for its use in severe bronchiolitis. A randomised controlled pilot study of the use of a bovine surfactant (survanta) in 9 ventilated infants with RSV bronchiolitis found a significant improvement in oxygenation at 60 hours compared to 10 controls treated with air placebo (Tibby et al., 2000). There was a

significant reduction in lung compliance and a corresponding increase in respiratory resistance at 30 hours in the placebo group but not the treatment group. These findings warrant further evaluation in a larger study.

1.2.6.1 Positive pressure ventilation

Positive pressure ventilatory support was first reported in the treatment of bronchiolitis-associated respiratory failure in the 1960s as this mode of ventilation was beginning to gain wide use. Downes and Striker (1966) reported its use in a cohort of 86 children, 23 of whom had respiratory failure due to bronchiolitis, acute asthma or pneumonia. Respiratory failure was defined using the following criteria:

1. Decreased or absent inspiratory breath sounds.
2. Severe inspiratory retractions and use of accessory muscles.
3. Cyanosis in 40% ambient oxygen.
4. Depressed level of consciousness and response to pain.
5. Poor skeletal muscle tone.

The presence of any 3 of these criteria for one hour was invariably found to be associated with respiratory acidosis ($PaCO_2$ > 65 mm Hg) and was used as an indication for starting PPV. All 23 children with respiratory failure (including 5 infants with bronchiolitis) who would normally have been expected to progress to circulatory arrest, recovered after receiving mechanical ventilation.

The definition of respiratory failure used by Downes and Striker reflects a previous focus on oxygenation as the essential criterion. A more contemporary definition of respiratory failure distinguishes between a failure in gas exchange manifest as hypoxaemia (PaO_2 < 8.0kPa; Type I respiratory failure) and ventilatory failure manifest as hypercapnia ($PaCO_2$ > 6.0kPa; Type II respiratory failure) with or without hypoxaemia (Roussos and Koutsoukou, 2003).

Outwater and Crone (1984) retrospectively evaluated 15 infants aged 2-12 weeks who had presented with bronchiolitis-associated respiratory failure and were managed with PPV; none had preceding chronic lung or heart disease. All infants survived to discharge with no clinically apparent respiratory sequelae.

In another retrospective review, Lebel et al. (1989) also found that PPV was well tolerated in 62 infants (over 10 years) with bronchiolitis-associated respiratory failure and all survived. This study too, excluded cases with preceding lung disease, congenital heart disease or multiple congenital malformations. Compared with previously well babies, these ‘high risk’ cases have been shown to have an increased risk of morbidity and death when they have been specifically evaluated (Navas et al., 1992, Stretton et al., 1992). These and other investigators have shown that PPV is effective in managing respiratory

failure and since its introduction it has become an established mode of treatment for children with severe bronchiolitis requiring respiratory support. Most studies have described a good outcome for infants who were previously healthy. However, complications can occur, the commoner ones are listed in table 1, and are found at a higher frequency among high risk groups (Stretton et al., 1992, Leclerc et al., 2001).

Table 1: Complications of intubation found in 100 consecutive cases admitted to a paediatric intensive care unit (Orlowski et al., 1980)

1. Post extubation stridor
2. Obstruction of tube from inspissated mucus
3. Obstruction from kinking of tube
4. Endobronchial intubation
5. Accidental extubation
6. Gastric distension
7. Nasal, oral or neck ulceration
8. Laryngotracheal ulcerations, granulomas, stenoses
9. Infection
10. Pneumothorax, pneumomediastinum
11. Atelectasis
12. Pneumonia
13. Oxygen toxicity
14. Tracheitis at post mortem
15. Cardiopulmonary arrest
16. Asphyxia with temporary or permanent brain injury
17. Death

1.2.6.2 Ventilator associated lung injury (VALI)

Ventilator-associated lung injury (VALI) is a term that describes a range of lung complications arising from PPV, which have become increasingly evident in recent years. The potential for pressure-induced damage (barotrauma) from the use of mechanical ventilation has been known for several decades (Mellins et al., 1972). What has

become clear more recently, from studies in adults and in animal models, is that more subtle lung injury can result from alveolar overdistension (volutrauma) and manifest as increased alveolar-capillary permeability (Slutsky, 1999, The ARDS Network, 2000). There has also been recognition of the effects of increased cytokine release from injured lungs which may have systemic effects in addition to further exacerbating lung injury (biotrauma) (Tremblay et al., 1997, Ranieri et al., 1999, Cheng et al., 2002).

Evaluation of positive pressure ventilatory strategies on the effects of cytokine release has been carried out in a randomised trial of 37 adults requiring PPV for acute respiratory distress syndrome (ARDS) (Ranieri et al., 1999). A lung protective strategy of tidal volume and positive end expiratory pressure (PEEP) selected on the basis of the flow volume curve (study group) was compared with a ventilatory strategy designed to achieve maximum oxygenation and normal $paCO_2$ without worsening haemodynamics (control group). Tidal volumes were significantly lower in the lung protective strategy (7.1ml/kg [SD 1.1] versus 11.1ml / kg [SD 1.3]; $p<0.001$) as was peak inspiratory pressure (24.6 cm H_2O [SD 2.4] versus 31.0 cm H_2O [SD 4.6], $p< 0.001$). PEEP was significantly higher in the lung protective strategy group (14.8 cm H_2O [2.7] versus 6.5 cm H_2O [1.7], $p< 0.001$). Pre-randomisation levels of the cytokines (tumour necrosis factor [TNF] α, Interleukin [IL]-1β, IL-6 and IL-8) did not differ between the groups in either broncho-alvealar fluid or serum.

Thirty-six hours after study entry, the lung protective strategy was associated with a significant reduction from baseline levels in the cytokines in broncho-alveolar fluid ($p<0.05$ to $p<0.001$), whilst in controls the cytokines had increased ($p<0.05$ to $p<0.001$). Compared to controls, the levels of cytokines and polymorphonuclear cells in broncho-alveolar fluid were significantly lower in the lung protective group at 36 hours post randomisation ($p<0.05$). Post hoc analysis found that the lung protective strategy was associated with a significantly higher mean number of ventilator-free days (12 days [SD 11] versus 4 days [SD 8]; $p<0.01$) and a non-significant lower mortality (38% versus 58%; $p=0.19$). These results suggest that positive pressure ventilation is associated with an inflammatory response that may be attenuated by a lung protective strategy of higher PEEP (to maintain alveolar opening and minimise collapse) and low tidal volumes (to reduce lung injury due to over distension). The clinical implications of a raised cytokine response have not been evaluated in this study but interesting evidence is provided to show that mechanical ventilation may be associated with lung injury independent of the condition for which it is being used.

A multi-centre randomised trial of 861 adults with acute lung injury and acute respiratory distress syndrome (ARDS) compared traditional ventilation strategy, using tidal volumes of 12mls/ kg, with a strategy of low tidal volumes of 6 mls/ kg (The ARDS Network, 2000). Ventilatory

rates were significantly higher in the low tidal volume group (29± 7 versus 16 ± 6 on day 1) and the mean $PaCO_2$ was greater (4-7 mm Hg higher than the traditional ventilation strategy group). The use of low tidal volumes was associated with a 22% reduction in mortality, significantly more ventilator-free days and significantly less multi-organ failure. There were no significant differences in the rates of barotrauma between the two groups - defined as pneumothorax, subcutaneous emphysema, pneumomediastinum, or a pneumatocele greater than 2 cm in diameter. These findings suggest that a ventilatory strategy involving excessive alveolar distension is associated with increased lung injury resulting in significant morbidity and mortality in adults. Complications associated with PPV have prompted some investigators to evaluate other less invasive modes of ventilation.

1.2.6.3 Continuous positive airway pressure (CPAP)

Continuous positive airway pressure (CPAP) is another commonly used mode of respiratory support for infants with bronchiolitis-associated respiratory failure which has been employed since the 1970's. Its main advantages over IPPV are that it can be delivered non-invasively (via nasal prongs) thereby avoiding the complications associated with intubation, and can be used without the infants needing to be sedated. A number of uncontrolled studies have found CPAP to be effective in bronchiolitis (Beasley and Jones, 1981, Cahill et al., 1983, Soong et al., 1993) despite the pathophysiological process of the

illness involving air trapping, which CPAP might be expected to make worse. Beasley and Jones (1981) first reported the use of CPAP for bronchiolitis in a cohort of 23 infants; 14 received nasal CPAP via a short nasal cannula and 9 via an endotracheal tube (ET). All 23 infants showed clinical improvement with CPAP and survived to be discharged. One infant suffered a pneumothorax, which was drained. It is noteworthy that CPAP was started at an earlier stage in these infants, before the development of uncompensated respiratory failure, than was PPV in a previous cohort. The authors observed that in the 5 years before they began to use CPAP, 288 infants were admitted with bronchiolitis and 13 were managed with PPV. In the 5 years after its introduction, just 2 infants (both with congenital heart disease) out of 305 with bronchiolitis required PPV. This study suggested that, if started early, CPAP might be an effective mode of respiratory support for bronchiolitis.

An uncontrolled study (Cahill et al., 1983) of 7 infants with bronchiolitis found that 6 could be managed successfully with nasal CPAP (NCPAP). One required intubation and mechanical ventilation, having shown no improvement after one hour on NCPAP. Soong et al. (1993) similarly found nasal CPAP to be effective in 10 out of 11 children with impending respiratory failure from bronchiolitis; one child with immunodeficiency required intubation and ventilation after showing no improvement on nasal CPAP.

It is postulated that CPAP works by keeping small airways open throughout the respiratory cycle. Paradoxically this reduces hyperinflation and air trapping and results in improved gas exchange (Soong et al., 1993). Studies have found CPAP to be relatively free of complications although pneumothoraces can occur. Children with very severe bronchiolitis may still require intubation and mechanical ventilation, as CPAP may be less effective than PPV once exhaustion and respiratory failure have developed. There are no randomised trials comparing the use of CPAP with other modes of ventilatory support for bronchiolitis.

1.2.6.4 Continuous negative extrathoracic pressure

Continuous negative extrathoracic pressure (CNEP) has been used as respiratory support in adults and children for a number of disorders but its use in children with bronchiolitis is limited to work by one team of doctors at two centres. Their work has resulted in 4 reports, 2 of them in abstract form only (Al-balkhi et al., 2005, Samuels and Southall, 1989, Linney et al., 1997, Hartmann et al., 1994b). Samuels and Southall (1989) reported their findings of an uncontrolled trial in 88 infants and young children with respiratory failure due to a variety of causes; most had either bronchopulmonary dysplasia [n=47] or respiratory distress syndrome [n=13] but 7 were reported to have ‘bronchiolitis or asthma’. For the group as a whole, the use of CNEP was found to result in a 15% median reduction in FiO_2 after 2 hrs

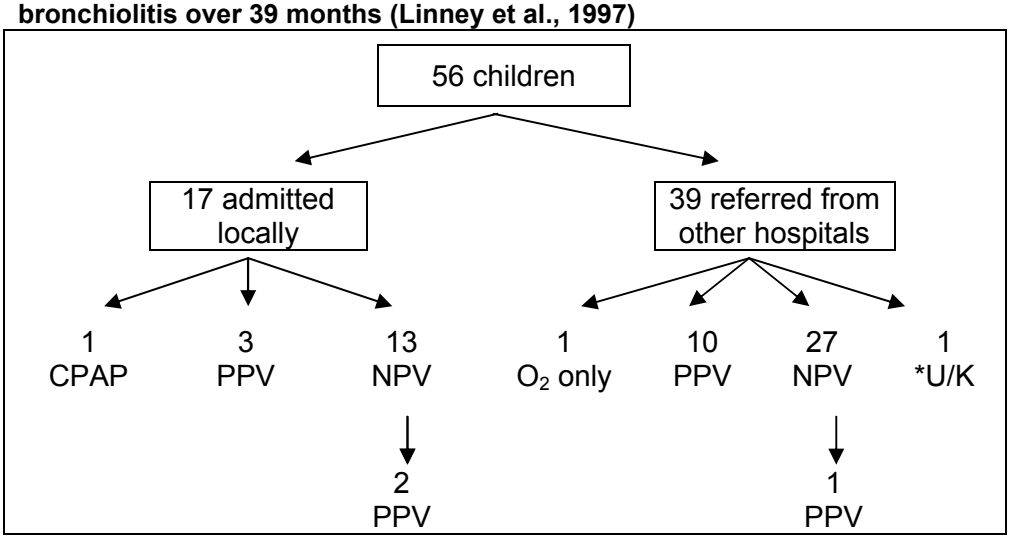
(range 0 -20%) and a 20% reduction at 48hrs (range 2 -79%). CNEP was reported to facilitate extubation in 28 out of 40 intubated children (no specific data are provided to substantiate this) and no potential complications such as fluid retention, pneumothorax or reflux with aspiration were experienced. Fifty-four of the 88 patients survived and were discharged, including 6 children who received long-term ventilatory support at home with CNEP. This study suggests CNEP may be an effective form of respiratory support but the lack of a control group reduces the significance of the findings.

Hartmann et al. (1994b) reported, in abstract form, the findings of a randomised controlled pilot study of 33 infants with bronchiolitis who needed ≥ 40% oxygen to maintain saturations between 96-99%. Fifteen infants were assigned to receive CNEP and 18 to conventional treatment. Administered oxygen was reduced to ≤ 30% within 1 hour of treatment for 4 children in the CNEP group with no change observed in the control group. There was no difference in the overall duration of oxygen therapy between the two groups. One child in the control group required intubation and ventilation and another required CPAP. None of the children treated with CNEP required intubation. The low rate of intervention in the control group and the criteria for selection of subjects ($FiO_2 \geq 0.4$) suggest that most of the children receiving CNEP would not have needed respiratory support had they not received it. CNEP was used predominantly to avoid intubation and PPV in this group of patients rather than as ‘rescue’ therapy. The small numbers involved

and lack of reported detail makes it difficult to draw conclusions from this study about the role of CNEP in bronchiolitis.

The other abstract report of the use of negative pressure ventilation (NPV) for bronchiolitis was of an uncontrolled study by Linney et al. (1997) and describes the outcome of 56 children with bronchiolitis referred to the paediatric intensive care unit at the NSH over 39 months (Figure 1). Intermittent negative extrathoracic pressure (INEP) with pressures of -20 to -30cm H_2O was used in addition to CNEP in some children.

Figure 1: Summary of the management of children admitted to NSH with bronchiolitis over 39 months (Linney et al., 1997)



* 1 child is unaccounted for in the abstract (U/K = Unknown)

Of the 56 children, 29 were referred to PICU because of severe respiratory distress, 21 for recurrent apnoea and 6 for other unspecified symptoms. Thirteen children were intubated and ventilated, either at or before retrieval. Of the 40 children treated with NPV as their primary respiratory support, 3 (7.5%) subsequently needed intubation and

another 5 (12.5%) were managed with nasal CPAP and NPV combined. The authors suggest that the use of NPV may be associated with reduced intubation rates, presumably based on their previous experience of most of these children needing intubation. Caution is required in interpreting these data because there is no control group.

A retrospective review (Al-balkhi et al., 2005) was conducted of the paediatric intensive care unit databases and case notes of 52 children with bronchiolitis-related apnoea admitted to two centres (NSH, QMC). NPV was used in addition to other standard treatment modalities: PPV, CPAP and methylxanthines, for infants admitted to NSH. Infants admitted to QMC received standard treatment modalities but not NPV. All 31 infants at NSH received respiratory support (23 NPV, 8 PPV) and 19 of 21 infants at QMC received respiratory support (18 PPV, 1 CPAP). There were no significant differences between the two groups in terms of neonatal data or bronchiolitis illness variables. The use of NPV was associated with a significantly reduced rate of intubation (26% v 86%; $p < 0.001$) and shorter median duration of stay on PICU (2 days v 7 days; $p < 0.001$). There was an increased use of methylxanthines at NSH (54% v 28%; $p = 0.06$) which could be a confounding factor in the difference in intubations rates. Nevertheless, the data suggest that the use of NPV was associated with lower rates of intubation and PPV as well as a shorter stay in PICU in the infants studied.

1.3 Outcome following bronchiolitis

1.3.1 Reactive airway disease

The long-term outcome following bronchiolitis has been extensively investigated and an association with subsequent reactive airway disease (RAD) has been found by most studies (Tables 2-5). RSV is the commonest cause of bronchiolitis and has been found most frequently to have an association with RAD but recent work suggests that rhinovirus may have an even stronger association with RAD than RSV (Kotaniemi-Syrjanen et al., 2003). Numerous studies have assessed the prevalence of RAD using a variety of criteria including: rates of wheezing, frequency of other respiratory tract illness, use of bronchodilators and lung function abnormalities. Uncontrolled studies have reported rates of wheezing as high as 75% in children in the first 2 years following their bronchiolitic illness (Table 2). Controlled studies however, have reported rates of wheezing of 34-50% depending on the age at follow-up (Table 3).

Sims et al. (1978) conducted a controlled retrospective study of 35 children aged 8 years who were admitted with RSV bronchiolitis as infants. The controls were matched for age, sex and socioeconomic status. Wheezing was reported to have occurred on one or more occasions in 18 (51%) children who had bronchiolitis in infancy compared to just one child (3%) in the control group ($p< 0.001$).

Pullan and Hey (1982) subsequently confirmed these findings in a larger population of 130 children who had been admitted to hospital with bronchiolitis in infancy and 111 controls of comparable age, sex and social class. When evaluated at 10 years of age, 42% of the index children had a history of wheezing at any age compared to19% of the controls ($p<0.001$).

Murray et al. (1992) similarly found, in a matched cohort study of 73 children admitted with bronchiolitis as infants, that 42.5% had wheezed in the previous 12 months compared to 15% of controls when assessed at 5.5 years (RR 2.8; $p<0.001$). A further study of 61 children from this cohort and 47 matched controls found significantly more wheezing (34% versus 13%; $p=0.018$), coughing (48% versus 17%; $p=0.002$) and a diagnosis of asthma (39% versus 13%; $p=0.004$) in the index children 9-10 years after their admission with bronchiolitis (Noble et al., 1997).

McConnochie and Roghmann (1989) prospectively evaluated a cohort of 153 children (51 with mild bronchiolitis, 102 matched controls) at 8 and 13 years of age, and found that a significant difference in wheezing at 8 years was no longer significant at 13 years of age.

The Tucson Children's Respiratory Study was a large prospective epidemiological study of respiratory illness in which 1246 children were enrolled at birth and assessed at 3, 6, 11 and 13 years of age (Stein et

al., 1999). Two hundred and seven children were identified who had RSV positive lower respiratory tract illness (LRTI) that did not require hospitalisation in the first 3 years of life. Compared to controls who had no LRTI in that time, the group with mild RSV-LRTI had a significantly increased risk of frequent wheeze by age 6 years (odds ratio, 4.3; 95% C.I. 2.2 - 8.7). The risk of frequent wheeze remained significantly greater at 11 years but there was no significant difference at 13 years of age.

Tables 2-5 summarise studies investigating the link between bronchiolitis and reactive airway disease. The different study designs and different definitions of wheezing account for much of the variation in the reported incidence of wheeze. Definitions used include: '**current wheeze**', defined as wheezing in the 12 months prior to follow up; '**frequent wheeze**', defined as more than 3 episodes in the last year and '**any wheeze**', defined as wheezing at any stage following the bronchiolitis illness. Some studies have only included wheezing episodes that have been verified by a doctor (Hall et al., 1984, Welliver and Duffy, 1993).

1.3.2 Lung function abnormalities

1.3.2.1 Spirometry

Most studies that have included spirometric tests in the assessment of children after bronchiolitis have found evidence of significant airflow limitation. Table 5 summarises the results from controlled studies. In that by Sims et al. (1978), compared with controls the post-bronchiolitis subjects had significantly lower peak expiratory flow rates (237.7 L/min versus 265.1 L/min; $p<0.02$) and forced expiratory volume in 0.75 seconds expressed as a percentage of forced expiratory capacity ($FEV_{0.75}$/ FVC x 100; 83.2% versus 87.3%; $p<0.05$).

Mok and Simpson (1984) conducted a case-control study of 200 children 7 years after their admission in infancy with lower respiratory tract infection. Bronchiolitis was the index illness in 104 of these children of whom 102 were able to perform lung function tests at follow-up. An equal number of controls with no history of respiratory illness in infancy were recruited from the same school as the index cases and matched for age, sex and if possible height. Children who had suffered bronchiolitis had significantly lower % predicted $FEV_{0.75}$ (87% versus 92.6%; $p \leq 0.01$), lower FEV_1: FVC ratio (0.88 versus 0.91; $p \leq 0.01$) and lower % predicted FEF_{25-75} (89.1 versus 101.3; $p \leq 0.01$) compared to controls at age 7 years.

Stein et al. (1999) reported findings from the Tucson Children's Respiratory Study in which 110 children who had suffered RSV- LRTI before 3 years of age were evaluated at 11 years of age with baseline and post bronchodilator forced expiratory volume (FEV_1). They were found to have significantly lower FEV_1 compared to 189 children who had had no LRTI ($p=0.001$) and were significantly more likely to respond to bronchodilators (odds ratio 2.4 [95% C.I. 1.0-5.8], $p \leq 0.05$).

Other studies have reported airflow limitation following bronchiolitis (Pullan and Hey, 1982) and (Noble et al., 1997). Increased bronchial hyperactivity determined by the response to methacoline, histamine or bronchodilators has also been reported in controlled (Pullan and Hey, 1982) and uncontrolled studies (Sly and Hibbert, 1989, Welliver and Duffy, 1993, Gurwitz et al., 1981). Pullan and Hey (1982), compared a cohort of children 10 years after bronchiolitis with controls; they found that 19 out of 102 index children had a positive histamine challenge (fall in FEV_1 > 20% at histamine concentrations <16g/l) compared to 6 out of 104 controls ($p<0.01$). Thirteen index children had a fall in FEV_1 >15% following exercise compared to 5 controls ($p<0.05$). Evidence of bronchial lability was found using one or other measure in 26 of 105 (25%) index children and 7 of 106 (7%) controls ($p< 0.001$).

1.3.2.2 Lung volumes and airway resistance (R_{aw}) - Plethysmography

Few outcome studies of children following bronchiolitis have used plethysmography to evaluate airway resistance, although it is the 'gold standard' method for assessing airway disease. It is difficult to perform in young children and the equipment required is very expensive. Stokes et al. (1981) prospectively studied 22 infants who had needed admission for bronchiolitis. They measured thoracic gas volumes and airways resistance by plethysmography during convalescence (between 1 and 18 days following admission), at 3- 4 months and at 12 -15 months after admission. Fourteen out of 19 infants were assessed to be hyperinflated during convalescence, with thoracic gas volume measurements greater than 40ml/kg; the expected mean value being 32.8ml/kg. Seven of 18 infants remained hyperinflated at 13 months. Eleven of 15 infants studied at all three time points showed a mean fall in airway resistance of 34% over the study period; 2 were unchanged and 2 rose by 60%. The lack of a control group, however, limits the significance of these findings.

Gurwitz et al. (1981) evaluated 48 children in an uncontrolled, retrospective study 10 years after admission with bronchiolitis and measured lung volumes, airway resistance, spirometry and methacholine responses. Fifty seven percent of children (27/47) had a positive methacholine challenge. Total lung capacity (TLC) was raised in 3 children and the residual volume/ total lung capacity ratio was

raised in 20 children compared to values obtained on normal children tested in their laboratory.

Henry et al. (1983) evaluated 55 children in an uncontrolled prospective study 2 years after admission with bronchiolitis. They measured thoracic gas volumes (TGV), airways resistance (R_{aw}) and total respiratory resistance (R_t) – using the forced oscillation technique before and after nebulised salbutamol. Twenty-two of 40 children able to complete lung function assessments were found to have a TGV more than 120% of the predicted value for weight (hyperinflated). In 9 children airways resistance fell more than 15% following salbutamol. Once again the study findings are limited by the lack of a control group.

Noble et al. (1997) evaluated 61 children from an original cohort of 101 infants, 9 -10 years after recruitment into a prospective study of outcome following admission with bronchiolitis. At the assessment at 5.5 years, 73 controls were recruited to match the 73 index children who were still available for follow-up (Murray et al., 1992); at the 9-10 year follow-up 47 of the controls were again available for assessment. Total lung capacity (TLC), residual volume (RV) and airways resistance (Raw) were measured by total body plethysmography in addition to spirometry and a histamine challenge. Measurements of TLC and RV were not significantly different between index cases and controls but

airway resistance (R_{aw}) was significantly higher in index cases (2.87 $cmH_2O/L/S$ versus 2.35$cmH_2O/L/S$; p=0.002).

These studies show that children who have had bronchiolitis have an increased prevalence of RAD, which returns close to that of the normal population by early adolescence. Evidence from studies which have included lung function testing suggest that there may be hyperinflation in the early years after bronchiolitis and increased airways resistance may still be evident after 10 years.

Table 2: Uncontrolled prospective or retrospective studies showing an increased frequency of reactive airway disease following bronchiolitis

First author (Year)	No of cases	Age at follow up (yrs)	Prevalence of wheezing	Definitions of wheeze	Lung function tests done
Renzi et al. (1997)	26	0.6	58%	Any wheeze	-
Stokes et al. (1981)	18	1	50%	Any wheeze	Lung volumes and airway resistance
Bont et al. (2000)	50	1	58%	Recurrent wheeze	-
Henry et al. (1983)	55	2	75%	Any wheeze	-
Korppi et al. (1993)	80 76	1 -2 2 -3	76% 58%	Recurrent wheeze	-
Bont et al. (2004)	106	3	60% 42%	Any wheeze Wheeze in last 12 months	-
Webb et al. (1985)	81	3.5	59%	Current wheeze	-
Rylander et al. (1988)	67	4 -7	64%	Any wheeze	Spirometry
Eisen and Bacal (1963)	63	4 -14	46%	Any wheeze - (asthma / previous recurrent wheeze)	-
Sly and Hibbert (1989)	35	5	71%	Asthma	Spirometry pre & post histamine challenge
Welliver and Duffy (1993)	43	7-8	60% 33%	Any wheeze (physician diagnosed) Wheeze in last 2 yrs	Spirometry pre and post methacoline/ bronchodilation
Hall et al. (1984)	29	8	45%	Any wheeze (physician diagnosed)	Spirometry
Gurwitz et al. (1981)	48	9-10	29%	Recurrent wheeze	Spirometry pre and post methacoline, lung volumes and airway resistance

Table 3: Retrospective controlled studies indicating a link between bronchiolitis and later reactive airway disease

First author (Year)	Number of cases / controls	Age at follow up (years)	Prevalence of wheezing	Significance (p)	Definition of wheeze
Osundwa (1993)	70 / 70	2	44% vs 12.9%	<0.001	Recurrent wheeze
Murray et al. (1992)*	73 / 73	5.5	42.5% vs 15%	<0.001	Current wheeze
Mok and Simpson (1984)	104 / 104	7	44.2% vs 18.3%	< 0.001	Any wheeze
Sims et al. (1978)	35 / 35	8	51% vs 3%	< 0.0005	Any wheeze
McConnochie and Roghmann (1984)	59 / 177	8	44.1% vs 13.6%	< 0.001	Wheeze in last 2 yrs
Pullan and Hey (1982)	130 / 111	10	42% vs 19%	< 0.001	Any wheeze
Noble et al. (1997)*	61 / 47	10	34% vs 13%	0.018	Current wheeze

Table 4: Prospective controlled studies indicating a link between bronchiolitis (or RSV lower respiratory tract infection before age 3 years) and later reactive airway disease

First author (Year)	Number of cases /controls	Age at follow up (years)	Incidence of wheezing	95% CI	Significance (p)	Definition of wheeze
Sigurs et al. (1995)*	47 / 93	1 3	RR: 2.5 RR: 1.9	1.40 - 4.47 1.27 - 2.69	0.003 0.003	Any wheeze
Sigurs et al. (2000)*	47 / 93	7.5	RR: 1.98 RR: 17.81	1.40 - 2.79 4.31 - 73.54	<0.001 <0.0001	Any wheeze Current wheeze
Stein et al. (1999)	68 / 601 56 / 489 79 / 555 49 / 420	6 8 11 13	OR: 4.3 OR: 1.9 OR: 2.4 OR: 1.4	2.2 - 8.7 0.9 - 4.2 1.3 - 4.6 0.7 - 2.6	<0.001 NS <0.01 NS	Frequent wheeze

*Includes children from the same cohort, RR = Risk ratio, OR = Odds ratio, CI = Confidence Intervals, NS = Not significant.

Table 5: Lung function results from controlled studies of outcome following bronchiolitis

First author, Year)	Number of cases /controls	Age at follow-up (years)	Lung function tests [Mean values: cases / controls]		Significance (p)	Other outcome
Murray et al. (1992)*	73 / 73	5.5	PEFR (% pred) $FEV_{0.75}$ (% pred) FEV_1 (% pred)	[96.2 / 97.8] [94.7 / 99.9] [96.4 / 100.1]	NS NS NS	
Mok and Simpson (1984)	102 / 102	7	$FEV_{0.75}$ (% pred) FEV_1 (% pred) FEF_{25-75} (% pred) FEV_1 / FVC	[87.0 / 92.6] [90.7 / 94.8] [89.1 /101.3] [0.88 / 0.91]	< 0.01 < 0.05 < 0.01 < 0.01	▪ FVC - NS ▪ 10% fall in PEFR - NS
Sims et al. (1978)	35 / 35	8	PEFR (l/min) FEV_1 / FVC (%)	[237.3 / 265.1] [83.2 / 87.3]	< 0.02 < 0.05	▪ $FEV_{0.75}$ - NS ▪ FVC - NS
Pullan and Hey (1982)	130 / 111	10	PEFR (l/min) FVC (litres) FEV_1 (litres) MEF_{25-75} (litres) FEV_1 / FVC (%)	[301 / 335] [2.26 / 2.38] [1.81 / 2.01] [1.90 / 2.27] [80.5 / 84.6]	< 0.001 < 0.005 < 0.001 < 0.001 < 0.001	
Noble et al. (1997)*	61 / 47	10	PEFR (% pred) $FEV_{0.75}$ (% pred) FEV_1 (% pred) MEF_{50} (% pred) R_{aw} (cmH_2O/l/s)	[93.2 / 102.0] [88.6 / 94.0] [91.0 / 96.1] [85.5 / 100.4] [2.87 / 2.35]	< 0.001 0.01 0.03 < 0.001 0.002	▪ FVC - NS
Stein et al. (1999)	110 / 189	11	FEV_1 litres (baseline) FEV_1 litres (post bronchodilator)	[2.11 / 2.22] [2.26/2.31]	<0.001 NS	

*Includes children from the same cohort. FEV = forced expiratory volume (FEV_1 = in 1 sec, $FEV_{0.75}$ = in 0.75 sec), FVC = forced vital capacity, MEF_{25-75} or FEF_{25-75} = forced mid-expiratory flow (between 25% and 75% of FVC), R_{aw} = airways resistance, PEFR = peak expiratory flow rate, NS = Not significant.

1.3.3 Mechanism for link between RSV infection and reactive airway disease

The pathophysiological mechanisms by which RSV infection might cause reactive airway disease have not been fully elucidated despite convincing evidence from extensive research suggesting such a link. Three hypotheses have been postulated: first, that RSV infection damages the lung or alters host immunity resulting in RAD; second, that RSV infection unmasks an inherent susceptibility to RAD and third that host responses and the definition of bronchiolitis used accounts for the increased RAD.

1.3.3.1 RSV effect on host inducing RAD

Evidence to support the first hypothesis is provided in a study by Piedimonte et al. (1999), in which the authors used a rat model to investigate the effect of RSV on the sub-epithelial neural network of the airway mucosa (figure 2). The three main factors determining airway patency are smooth muscle constriction, mucosal oedema and mucous secretion which are in turn controlled by adrenergic, cholinergic and non-adrenergic-non-cholinergic (NANC) neural pathways. The NANC neural pathways consist of an excitatory (NANCe) component inducing smooth muscle contraction and an inhibitory (NANCi) component inducing relaxation. The effects of the NANCe pathways are mediated by neurotransmitters including the neuropeptide substance P and neurokinins A &B. Substance P acts at three receptor subtypes (NK-1

NK-2, NK-3) of which the NK-1 subtype appears to have the highest affinity for it (Piedimonte, 2001).

Piedimonte et al. (1999) studied the inflammatory response associated with the release of substance P in RSV-infected rats. They inoculated the tracheas of 5 rats with RSV and 6 with a virus-free medium; 5 days later they injected Evans blue-labelled albumin intravenously to measure extravasation of albumin from airway microvasculature and then infused the tracheas with vehicle alone, substance P or capsaicin (which stimulates endogenous release of multiple neuropeptides including substance P) in separate groups of rats. There was no significant difference in the extravasation of albumin between uninfected and RSV infected rats receiving vehicle alone. Extravasation (assessed by measuring optical density) was significantly increased in the RSV infected rats following infusion of substance P ($p<0.001$) and capsaicin, ($p<0.001$). The investigators further identified a 5 -fold increased expression of NK-1 receptors ($p<0.001$) in the airway and lungs of RSV infected rats compared to uninfected rats using RT-PCR techniques. These findings suggest that RSV LRTI in rats increases airway susceptibility to the inflammatory effects of substance P by upregulating NK-1 receptor gene expression. This model offers a potential mechanism for the observed effects of RSV in humans. Interestingly the authors also found that the neurogenically mediated inflammatory response in RSV-infected adult rats was most prominent

in the extra-pulmonary airways whilst in weanling RSV-infected rats it was most prominent in the intra-pulmonary airways. This observation probably reflects a maturational change in the distribution of NANCe fibres in the respiratory tract in rats which if true in humans might explain the difference in the acute effects of RSV infection in different age groups and the decline in RAD symptoms over time.

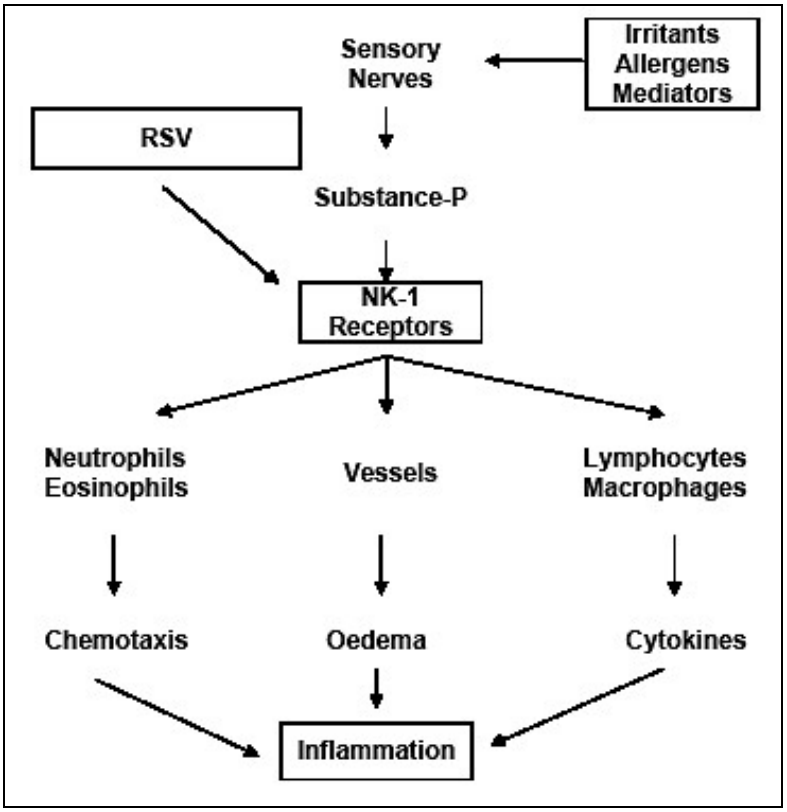


Figure 2: Diagram showing how RSV may increase neurogenic inflammation by upregulating NK-1 receptors (Piedimonte, 2001)

1.3.3.2 RSV unmasks host factors

Supporting the second hypothesis, that RSV infection is a provoking event in children with an inherent risk of wheezing, is the observation that diminished lung function before bronchiolitis is a risk factor for

wheezing afterwards (Young et al., 1995, Martinez et al., 1988). Martinez et al. (1988) evaluated 124 children enrolled as newborns into the Tuscon Children's Respiratory Study who had lung function tests before any lower respiratory tract illness (LRTI). The risk of wheezing at one year of age was 3.7 times higher (95% CI, 0.9 -15.5; p=0.06) among infants whose respiratory pre-morbid conductance was in the lower third, compared to those whose conductance was in the upper two-thirds. Similar findings were described by Young et al. (1995) in a prospective study of 253 children. They performed respiratory function tests (maximum flow at functional residual capacity [V_{max}FRC] using thoracic compression) at 1, 6 and 12 months of age. In 17 infants who had bronchiolitis during the first 2 years of life, a significant trend for the baseline V_{max}FRC values to be in the lowest tercile was observed at 5 weeks of age (Young et al., 1995).

1.3.3.3 Host factors determine RSV illness and subsequent RAD

An alternative view of how host responses may account for the increased prevalence of RAD following RSV bronchiolitis is that it is largely due to the definition of bronchiolitis used. It is postulated that a definition of bronchiolitis that specifies wheeze as an important diagnostic symptom, as is generally used in North America, selects out children with a predisposition to asthma and an increased likelihood of subsequent wheezing (Everard, 2006a). The UK and some European countries use a definition of bronchiolitis that includes signs of an upper

respiratory tract infection (URTI) associated with lower respiratory tract obstruction and characterised by the presence of crepitations. In North America and other parts of Europe, acute bronchiolitis is used to describe an infant presenting with their first wheezing illness associated with an URTI. In the UK, a number of the latter infants would have previously been described as having ‘wheezy bronchitis’, a term which has since been replaced by ‘viral induced wheeze’. The clinical progress of these children usually involves increased wheezing in the first few years of life which does not persist beyond the first decade, similar to that observed in infants with presumed RAD post bronchiolitis (Everard, 2006b).

This hypothesis is supported by a prospective cohort study by Elphick et al. (2007). The effect of 2 different phenotypes of acute RSV illness on subsequent outcomes was evaluated in 56 infants with RSV LRTI and 94 controls. The RSV infants were divided into those with bronchiolitis (RSVB) characterised by widespread crepitations with or without wheeze [n=42] and those with wheeze alone (RSVW) - viral associated wheeze [n=14]. At 3 years of age, 37 of the RSV cohort (28 RSVB, 9 RSVW) and 77 controls were assessed with a respiratory questionnaire and skin prick testing (SPT). Children with RSVW were significantly more likely to have wheezed most days in association with colds odds ratio 42.0 (95% C.I. 3.5 - 501) compared to children with RSVB 9.9 (95% C.I. 1.0 -101). There was no significant increase in

allergic sensitisation on SPT in the RSV group as a whole when compared to controls. However, within the RSV subgroups, allergic sensitisation was more common in the RSVW group. Eight of the 77 controls (10%), 2/28 (7.1%) of the RSVB and 2/9 (22.2%) of the RSVW groups had evidence of allergic sensitisation defined as SPT positive to 1 or more allergens. The group with RSVW also had increased healthcare utilisation compared to the RSVB group defined as visits to general practitioners and use of inhaled corticosteroids. These data suggest that host factors may determine the pattern of illness associated with RSV LRTI and influence the frequency and severity of subsequent symptoms. However, due to the small numbers studied in the RSV subgroups, caution is required in interpreting these findings.

1.3.4 Effect of RSV prophylaxis on respiratory outcome

If RAD is largely a consequence of RSV infection and not just of an inherent susceptibility, it should be possible to minimise it by the acute management of the infection or by the use of prophylaxis. Promising results have come from studies in rats. Piedimonte et al. (2000) gave Palivizumab to rats 24 hours before infecting them with RSV. They again measured microvascular permeability using an Evans blue-labelled tracer followed by infusion of capsaicin 5 days after inoculation with RSV. They found that palivizumab suppressed neurogenic inflammation in RSV-infected rats to the same level as that found in infection-free controls. The authors postulated that by preventing the

increased neurogenic inflammatory response at the time of RSV infection, it might be possible to avoid the long term RAD.

A study comparing 13 children who received the prophylactic agent, RSV-IVIG, and 26 controls who did not, found that the FEV_1/ FVC ratios were significantly higher (p=0.02) 7-10 years later in the treatment group. There was significantly less atopy (p =0.04) and a lower likelihood of 'asthma attacks' (p =0.03) (Wenzel et al., 2002). These results suggest that it may be possible to reduce the incidence of RAD by preventing or ameliorating RSV infection but more data are needed to confirm these findings.

1.3.5 Effect of acute therapies on respiratory outcome

The immediate benefits of treatments for acute bronchiolitis, apart from oxygen and fluids given as necessary, have remained largely unproven. However, there has, been interest in the possibility of reducing the burden of post-bronchiolitis RAD by modifying the initial infection. Therapies that have been evaluated for their long-term respiratory outcome include ribavarin, corticosteroids and leukotriene receptor antagonists.

1.3.5.1 Ribavarin

Long et al. (1997) conducted a prospective randomised study of ribavarin or placebo in 60 infants hospitalised with RSV bronchiolitis, to determine its effect on the incidence of lower respiratory tract infection and lung function. They found no significant difference between the groups in the rates or severity of respiratory tract illness, oxygen saturation, spirometry or peak expiratory flow measurements 4-6 years after their initial illness.

In a 7 year prospective follow-up study, Rodriguez et al. (1999) evaluated outcome in 35 of 42 patients who had been randomly assigned to receive ribavarin or placebo during hospitalisation with RSV lower respiratory tract infection. Five were lost to follow-up immediately after discharge and 2 died during the initial admission. Follow-up included monthly phone calls, at least once yearly hospital assessments and lung function once children were 5 years old, including a methacholine challenge at 7 years. Over the period of study, 4 (17%) of the 24 ribavarin subjects had more than 1 wheezing episode compared to 6 (55%) of 11 controls (p=0.04). Nineteen patients (13 ribavirin and 6 controls) completed lung function tests; seven of the 13 ribavirin patients, but none of the 6 controls had normal lung function or just mild abnormalities (p=0.04). On methacholine challenge (7 ribavirin, 5 controls) there was a trend towards increased reactivity in the controls (p=0.07). The high drop out rate and small

numbers included in this study require cautious interpretation of these findings.

A prospective study by Edell et al. (2002) also evaluated long-term respiratory outcome, in 49 infants treated with ribavarin in the early phase of severe bronchiolitis. Infants aged less than 6 months admitted with RSV bronchiolitis were randomly assigned to receive conservative treatment (bronchodilators, corticosteroids, antacids and feed thickeners) or additional treatment with high dose ribavarin. Infants were recruited if the onset of symptoms was within 5 days. Forty-five infants were followed up for 12 months (24 treated with ribavarin; 21 controls) with fortnightly telephone calls and clinical examination by a respiratory physician as required. Compared with controls the ribavarin group had fewer episodes of reactive airway disease (2.7 $\pm$ 2.3 versus 6.4 $\pm$ 4.2 episodes/ patient/ year) which were less severe (0.08 versus 1.09 episodes of moderate-severe illness / patient/ year). Treatment with ribavarin was associated with fewer in-patient days for respiratory illness; 6 of 21 patients in the control group were hospitalised for a total of 19 days compared to 2 of 24 patients in the ribavarin group for a total of 6 days ($p<0.05$).

Several factors may account for the differences in findings in the studies by Edell et al (2002) compared to those by Long et al (1997) and Rodriguez et al (1999). The study by Edell et al (2002) used

ribavarin at an earlier stage in the bronchiolitic illness and also used a combination of therapies including corticosteroids, which may have worked synergistically with ribavarin to produce a more significant effect than either therapy alone. Follow up in this study was for a much shorter period; 12 months versus 4-6 years/ 7 years. It remains unclear therefore, whether ribavarin does indeed have beneficial long-term effects on respiratory outcome following bronchiolitis.

1.3.5.2 Corticosteroids

Both systemic and inhaled corticosteroids have been evaluated for their long-term effect on respiratory outcome following bronchiolitis, most studies finding no benefit from their use. Studies of the use of inhaled corticosteroids have provided inconsistent results; most have found no long-term benefit but two Finnish studies did find significant differences in RAD between treated groups and controls.

A prospective randomised double blind placebo-controlled trial in 54 patients given prednisolone for 7 days found no difference between the groups in the incidence of transient, persistent or late onset wheeze during 5 years of follow-up (van Woensel et al., 2000).

Cade et al. (2000) conducted a randomised placebo-controlled trial of inhaled budesonide (1 mg) given twice daily in 161 hospitalised infants

with RSV bronchiolitis and continued for 2 weeks after discharge. They found no significant difference in the prevalence of wheezing, General Practitioner visits, respiratory-related hospital re-admission rates or bronchodilator use between the groups at follow-up 12 months later.

In a prospective randomised placebo-controlled study by Fox et al. (1999) 49 infants hospitalised with viral bronchiolitis were allocated to receive 200 micrograms of inhaled budesonide or placebo, twice daily for two weeks. The authors achieved full follow-up data of the 49 infants over 12 months. Twenty-one infants in the budesonide group reported symptom episodes compared to 12 in the control group ($p=0.03$). The authors concluded that, in the absence of a pharmacological explanation, the less favourable outcome in the treatment group was probably a 'type one error'. This study found no evidence that the use of inhaled budesonide reduced post bronchiolitis coughing and wheezing. A randomised controlled study by Wong et al. (2000) similarly found no benefit from the 3 month use of inhaled fluticasone during 12 months of follow-up.

Two studies showing a benefit from inhaled steroids are reported by Kajosaari et al. (2000) and Reijonen et al. (1996). The first was an open study of 117 hospitalised infants with RSV bronchiolitis who were randomised to 3 possible groups of treatment - Group I: symptomatic

treatment; Group II: 500 micrograms of nebulised budesonide three times a day for 7 days; Group III: 500 micrograms of nebulised budesonide twice daily for 8 weeks. Both treatment groups also received symptomatic treatment. Two-year follow-up was achieved in 109 infants. At 2 years, 14 of 38 infants (37%) who received symptomatic treatment alone were receiving asthma therapy compared with 7 of 39 (18%) in group II (p=0.006) and 4 out of 32 (12%) in group III (p=0.01). Similar results are reported by Reijonen et al. (1996) with the use of budesonide 500 micrograms twice daily for 8 weeks.

Most studies evaluating the use of either systemic or inhaled corticosteroids have found no long-term benefit. Inconsistencies in the findings may reflect heterogeneity of the study populations and differences in study methods. There is currently insufficient evidence to support the use of corticosteroids for prevention of RAD post bronchiolitis.

1.3.5.3 Leukotriene receptor antagonists

The association of RSV infection with an increased production of cysteinyl leukotrienes (Piedimonte et al., 2005) has prompted investigation into the possibility of leukotriene receptor antagonist use to reduce the incidence of later reactive airway disease. Bisgaard and Study Group on Montelukast and Respiratory Syncytial Virus (2003)

conducted a double blind randomised trial of montelukast or placebo in 130 infants aged 3 - 36 months with RSV infection needing hospital admission. Montelukast was started within 7 days of the onset of symptoms and given for 28 days. Follow-up data were available for 116 infants at 28 days after starting treatment and for 87 infants at 56 days. Those treated with montelukast had significantly more symptom-free days compared to controls (6 / 28 [22%] versus 1 / 28 [4%] days, p=0.015), significantly less cough (p=0.04) and significantly longer periods between respiratory exacerbations (p= 0.04) for the 4 week duration of treatment. There were no significant differences in outcome at the later follow-up at 56 days. These findings are promising even though the benefit found at 28 days was no longer apparent at 8 weeks. More studies are needed to evaluate the long-term effects of leukotriene receptor antagonists further. The potential benefit of leukotriene receptor antagonists used in this way deserves further evaluation.

1.3.6 Respiratory outcome after mechanical ventilation for bronchiolitis

There is surprisingly little evidence to suggest that bronchiolitis severe enough to need ventilation is more likely than mild bronchiolitis to be associated with respiratory sequelae. Outcomes in ventilated and non-ventilated groups have rarely been compared. In one uncontrolled prospective study of 29 children with bronchiolitis, Hall et al. (1984) found that the 4 infants needing ventilation all had recurrent lower

respiratory tract illness over 8 years of follow-up, compared to 9 (26%) of the 25 non-ventilated infants . Other measures of illness severity, such as apnoea, duration of oxygen requirement and length of hospital stay, were not associated with an increased risk of later lower respiratory tract illness. The small sample size and lack of controls limit the significance of these findings.

Priftis et al. (1990) retrospectively evaluated 19 children who had needed mechanical ventilation for severe bronchiolitis. Two patients had died at the time of their bronchiolitis and one later from spinal muscular atrophy. The median age of survivors at follow-up was 4.8 years (range 1.1 - 10 years). Parents completed questionnaires and General Practitioners provided relevant medical information. Nine (56%) of the 16 surviving children had wheezing after discharge and 6 (38%) had been diagnosed with asthma. The authors comment that these rates are similar to those reported in non-ventilated populations. As in the study by Hall et al. (1984), the small numbers and lack of controls severely limit the strength of evidence about the effect of ventilation during bronchiolitis on the rates of later wheezing.

1.3.7 Neurological outcome after mechanical ventilation for bronchiolitis

Adverse neurological outcome following bronchiolitis is rarely reported in the literature-; only 2 uncontrolled studies have been identified which provide limited data on this outcome measure.

Bray and Morrell (1982) conducted a retrospective uncontrolled study of 58 children who had survived after mechanical ventilation for a variety of conditions, including bronchiolitis. Between 1971 and 1978, 132 children were ventilated in the paediatric intensive care unit in Newcastle, UK; 66 (50% of the cohort) survived to discharge from hospital but 8 died later. The 58 long-term survivors were traced and 48 were examined for evidence of auditory, visual, behavioural, developmental and central nervous system abnormalities; data were obtained through postal contact or via general practitioners for the 10 children not attending for examination. The ages of children at ventilation ranged from <1 day to 7 years and at follow up was 1 year to 11 years. Seven percent of the cohort was found to have definite neurological or learning disability and a further 14% had equivocal scores on the Denver Developmental Screening Test (DDST). No neurological or intellectual impairment was found in 79% of the cohort. Thirteen of the 58 children had been ventilated for respiratory problems, which included bronchiolitis in an unspecified number. Eight of these 13 children had no apparent neurological or intellectual impairment at follow up; of the five found to have abnormalities, three

had been ventilated for bronchiolitis; one for apnoeic attacks and one for croup. Two of the three children ventilated for bronchiolitis later had febrile seizures but had no disability at follow up; the third child had spastic quadriplegia, epilepsy, visual impairment, behaviour problems and an abnormal DDST score (reported to correlate with IQ < 70). The authors concluded that abnormalities found in the 4 most severely disabled children resulted from the presenting illness or previous events rather than from their ventilation therapy- in support of this assertion they cited the example of a child with severe disability following bronchiolitis who at presentation had a capillary blood pH of 6.96 and pCO_2 of 20 Kpa.

The second study (Wren et al., 1982) is of 9 infants admitted to intensive care in a tertiary centre in Dublin during the 12 months of 1981. Six infants were intubated, of whom 5 were mechanically ventilated and one received CPAP via endotracheal tube. One with Pierre Robin sequence required a tracheostomy and was then able to breathe spontaneously; two were managed with nasal CPAP alone. One child who suffered a cardiac arrest was later found to have spasticity and neurodevelopmental delay, however; the child had had episodes of hypoglycaemia and twitching in the neonatal period which adds uncertainty as to the timing of the neurological injury.

The limited evidence from these 2 studies suggests that neurological injury may occur in severe cases of bronchiolitis that are associated with cardio-respiratory failure.

1.4 Negative Pressure Ventilation

1.4.1 History of Negative Pressure Ventilation

Negative pressure ventilation was first described in the early 1800s but was not widely used until 1928 when Drinker and Shaw developed a device that was found to be clinically useful (Drinker and Shaw, 1929). Over the next 30 years negative pressure ventilators (so-called 'iron lungs') were widely and successfully used to give respiratory support to patients with paralytic poliomyelitis (Thomson, 1997). Their popularity waned towards the end of the 1950s with the development of positive pressure ventilation, delivered through a tracheostomy or endotracheal tube, which was found to be more efficient. At the peak of a polio epidemic in 1952, one Copenhagen hospital observed a fall in mortality among polio patients from 87% to 42% in just 3 months following the introduction of positive pressure ventilation (Lassen, 1953). Between 1934-1944 the Blegdam hospital in Copenhagen treated 76 cases of polio-associated respiratory failure with NPV of whom 61 (80%) died. Between 1948 and 1950 the authors evaluated the use of a tracheostomy to manage upper airway obstruction in association with NPV and found the combination of therapies was associated with a worse outcome than with NPV alone as all 14 patients who had both

therapies died. In the first month of the 1952 polio epidemic 27 out of 31 cases (87%) managed with NPV died. Over the next 2 months bag ventilation via tracheostomy was used instead and was associated with 100 deaths in 250 patients (40% mortality). Negative pressure ventilation continued to be used by some investigators during the 1960's -70's and was found to be effective in neonatal RDS (Chernick and Vidyasagar, 1972, Outerbridge et al., 1972, Fanaroff et al., 1973). From the 1970's onwards it was no longer used routinely, having been largely replaced by positive pressure ventilation.

Non-invasive ventilation techniques have recently enjoyed renewed interest due to increased concern about the problems associated with invasive positive pressure ventilation, including the recognition of ventilator-induced lung injury (Slutsky, 1999). Both non-invasive positive pressure and negative pressure ventilation have been the focus of renewed interest. The original negative pressure ventilators had a number of problems; Drinker and Shaw's 'iron-lung' was bulky and cumbersome with limited access to patients, there were difficulties maintaining a thermal environment and a lack of protection of the upper airway meant its use was associated with upper airway obstruction in some patients (Corrado et al., 1996, Thomson, 1997). Problems with the neck seal included pressure sores and impaired jugular venous drainage. The concerns about the latter were heightened following a study by (Vert et al., 1973), which suggested a possible association of

post-haemorrhagic hydrocephalus with the use of a similar neck seal in children treated with the 'Gregory Box', a non-invasive continuous positive pressure device. The authors identified 6 infants with hydrocephalus from a cohort of 61 (50 survivors), who had been treated with CPAP for respiratory distress syndrome. In the 6 infants with hydrocephalus (diagnosed by air encephalography) superior sagittal sinus pressures were measured using a manometer connected to a needle inserted directly into the sinus. The authors found the sinus pressure was consistently increased by 3.6 - 8.6cm H_2O following the application of a loosely tied collar. In contrast the administration of 10cm H_2O of CPAP via a nasotracheal tube did not increase the sinus pressure by more than 1cm H_2O in the 3 cases evaluated. The authors concluded that the collar was probably causing a 'garrotting effect', resulting in raised intracranial pressure and hydrocephalus (Vert et al., 1973).

Technical improvements in recent years have overcome most of the problems associated with older versions of the negative pressure ventilator. A recently modified negative pressure ventilator was used at the North Staffordshire Hospital between 1993 and 1999 to treat children with bronchiolitis-associated respiratory failure. The device is described in detail in a report by Samuels and Southall (1989).

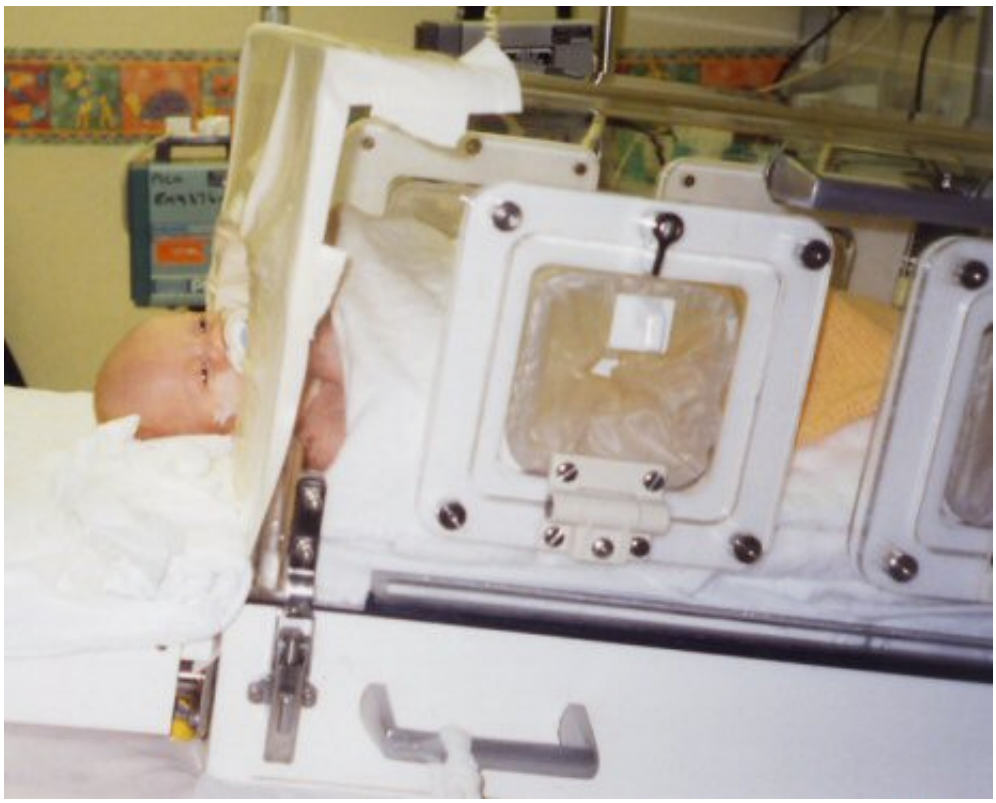


Figure 3: Picture of an infant in a negative pressure tank receiving nasal cannula oxygen

The depicted negative pressure tank is available in three sizes: neonatal (babies weighing < 4 kg), infant (3–8 kg) and toddler (5–20 kg). The baby's head protrudes through an arch in the top end of the chamber. The neck seal comprises a rectangular sheet of latex in which is cut a hole about two-thirds the cross-sectional area of the baby's neck; the elasticity of the latex allows a tight seal to be maintained without circumferential pressure. The various portholes allow access to the baby and provide entrances for monitoring leads and lines whilst maintaining sub atmospheric pressure within the chamber. Sub atmospheric pressure is generated within the chamber by a suction unit, which has a twin valve system allowing the provision of intermittent negative extrathoracic pressure (INEP) in addition to CNEP. The circulation of warm air (servo-controlled to the ambient

temperature) within the chamber allows the body temperature of small babies to be adequately maintained.

1.4.2 Principles and technique of Negative Pressure Ventilation

Negative pressure devices assist ventilation by applying sub atmospheric pressure around the thorax and abdomen causing the chest wall to expand and the lungs to inflate. Several devices are available and are either tank ventilators, which enclose patients up to their necks, or cuirass / jacket ventilators, which are applied to the chest and abdomen only. The cuirass ventilators are not available in a size small enough to use in small baby and so the tank ventilators are the only realistic mode of delivery of negative pressure support for babies. The modes of negative pressure that can be delivered are:

1. **Cyclical negative pressure** - negative pressure applied only during inspiration; in the expiratory phase the pressure is the same as atmospheric.

2. **Continuous negative extrathoracic pressure (CNEP)** - negative pressure applied continuously throughout the respiratory cycle

3. **Intermittent negative extrathoracic pressure (INEP) / CNEP** - intermittent cycles of increased negative pressure superimposed on a background of CNEP

4. **Negative / positive pressure** - a combination of negative pressure during inspiration and positive pressure during expiration.

1.4.3 Physiological effects of Negative Pressure Ventilation

Gappa et al. (1994) studied the effect of CNEP on passive respiratory mechanics and respiratory timing in 18 preterm infants recovering from neonatal respiratory distress syndrome. The aim of the study was to assess the physiological effects of CNEP in this population. Twenty infants were recruited and lung function testing was completed in 18 including compliance measured using the multiple occlusion technique (MOT), compliance and resistance measured by the single breath technique (SBT) and airflow measured with a pneumotachograph. Measurements were taken in atmospheric pressure and following the application of -6 cm H_2O of CNEP. A significant decrease in the respiratory rate (from 63.6 +/- 10.0 to 49.3 +/- 9.1 breaths / minute, $p< 0.0001$) was observed in all but 1 infant (n=18) during the application of CNEP. This reduction in respiratory rate was due to a 35% increase in the mean expiratory time (0.57 second pre CNEP, 0.77 second post CNEP, $p<0.0001$) which the authors attribute to increased tonic vagal activity caused by stimulation of stretch receptors. The mean compliance (C_{rs}) measured with the single breath technique, increased from 23.2 (SD 5.1) $mL.kPa^{-1}$ in atmospheric pressure to 27.1 (SD 4.7) $mL.kPa^{-1}$, ($p=0.006$) following the application of CNEP. The compliance

(C_{rs}) measured using the multiple occlusion technique did not change significantly. Further analysis showed that compliance was significantly increased in babies where the baseline measurement was low but not in babies whose baseline values were normal. There was no significant change in respiratory system resistance and minimal change in tidal volumes. The authors hypothesized that the application of CNEP results in the ventilation of previously collapsed lung and that a redistribution of lung volume from over distended units to recruited units improves compliance. They suggest the benefits are thereby achieved without a significant overall increase in lung volume.

Essa et al. (1994) performed a comparative study of the effects of CNEP and positive end expiratory pressure (PEEP) in anaesthetised piglets receiving positive pressure ventilation after saline lung lavage was used to induce lung injury. Thirteen piglets were randomly assigned to receive CNEP or PEEP which was increased at 15 minute intervals to 3, 6, 9 and then 12 cm H_2O (CNEP: -3,- 6, -9 and -12 cm H_2O). The peak inspiratory pressure (PIP) was adjusted to maintain a constant tidal volume and significantly higher values were required in the piglets receiving PEEP. No significant difference was observed in the effects of PEEP and CNEP on lung compliance, resistance, arterial oxygen pressure or cardiac output. The only significant difference observed was a lower end-expiratory lung volume (EELV) in the PEEP piglets at pressures of 3, 6 and 9 cm H_2O. The authors account for the

lower EELV in the piglets that received PEEP as probably a result of more severe lung injury in this group, evidenced by the trend towards lower compliance and higher resistance prior to commencing PEEP. An alternative explanation was a loss of volume in the PEEP piglets due to brief disconnection from the ventilator to allow measurement of EELV whereas the CNEP group continued to receive sub-atmospheric pressure during this procedure. They concluded that CNEP and PEEP are physiologically equivalent in an animal model; however, their data suggests that CNEP may have a beneficial effect of reducing the need for higher PIP when used in combination with positive pressure ventilation compared to PEEP.

The haemodynamic effects of negative pressure ventilation are dependent on the type of device used. Venous return to the heart is improved by the use of cuirass devices, which lower intrathoracic pressure relative to the rest of the body. Tank ventilators that enclose the whole body up to the neck do not generate a pressure difference between the thorax and lower parts of the body and thus the resulting effect on cardiac output is no different from that of positive pressure ventilators. The haemodynamic effects of the cuirass ventilators make them particularly useful in the management of children with low cardiac output following cardiac surgery.

Shekerdemian et al. (1997) conducted a prospective study to compare the effects of IPPV and NPV in 9 patients immediately after a Fontan procedure and in 9 patients undergoing cardiac catheterisation between 5 months and 15 years after Fontan-like procedures. Low cardiac output is a recognised complication of the immediate post operative recovery following a Fontan procedure but has also been reported to occur in some patients in the late convalescent period (Shekerdemian et al., 1997). All patients were intubated and ventilated with IPPV and received negative pressure ventilation for brief periods using the Hayek external high-frequency oscillator (cuirass type NPV). Pulmonary blood flow was measured using the Flick method during IPPV and again after starting NPV. In 6 patients further measurements were made after IPPV was reinstituted and after a second extended period (30- 45 minutes) of NPV. Pulmonary blood flow increased during the first period of NPV from 2.3±1.2 to 3.3± 1.9 $L \cdot min^{-1} \cdot m^{-2}$ (p=0.01) in acute patients and from 2.6±1.0 to 3.7±1.1 $L \cdot min^{-1} \cdot m^{-2}$ (p=0.01) in convalescent patients. Mean pulmonary blood flow for both acute and convalescent patients increased from 2.4±1.1 to 3.5±1.5 $L \cdot min^{-1} \cdot m^{-2}$ (p=0.003), with a mean increase of 42 ± 24%. The values reversed towards baseline after resuming IPPV. Following a second extended period of NPV in 6 patients the mean pulmonary blood flow increased by 53.6 ±17% (from 2.5±0.7to 3.8±1.2 $L \cdot min^{-1} \cdot m^{-2}$; p=0.01). During NPV there was no significant change in heart rate and the stroke volume for the group as a whole increased by 44% from 24.9±13 to 36.5±22 mL/m^2 (p=0.001). This study demonstrates that cuirass type NPV can

significantly improve pulmonary blood flow in patients following a Fontan procedure by encouraging venous return from the lower body thereby increasing stroke volume.

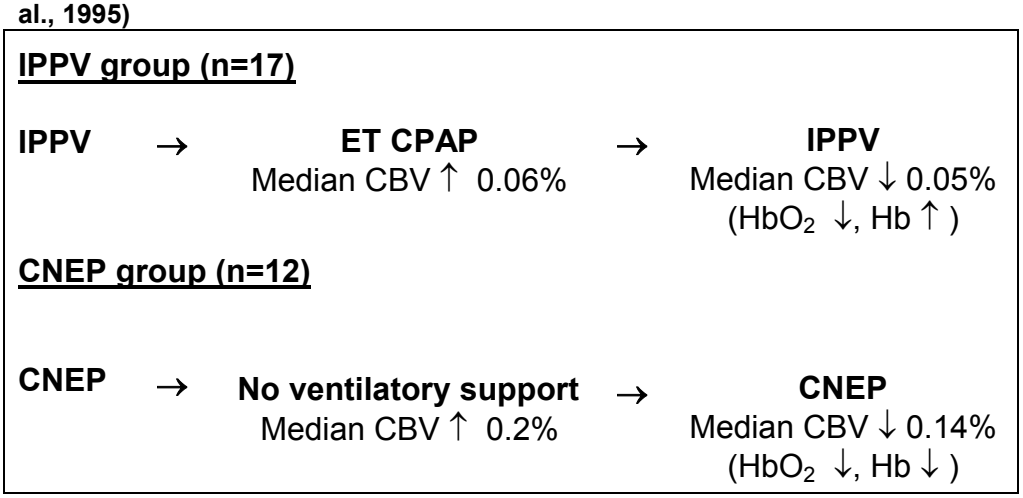
The same authors evaluated the haemodynamic effects of NPV in 23 children in the early post operative period following tetralogy of Fallot repair, using a similar study protocol (Shekerdemian et al., 1999). They were able to categorise the patients further according to the presence or absence of restrictive right ventriclular physiology, defined as antegrade diastolic pulmonary arterial flow present throughout the respiratory cycle during echocardiography. They found that, in the group as a whole, the use of NPV resulted in an increase in pulmonary blood flow of 39% after a 15-minute period of NPV and of 67% after an extended period of 45 minutes. They noted, however, that the effect was most marked in those with restrictive right ventricular physiology (n=8), who had an 84% increase in pulmonary blood flow during the extended period of NPV compared to a 50% increase in the non-restrictive group (n=15).

Palmer et al. (1995) studied the effects of positive and negative pressure on cerebral blood flow in 29 newborn infants; 12 receiving CNEP and 17 receiving IPPV, for either respiratory distress syndrome (n=25), bronchopulmonary dysplasia (n=3) or pneumonia (n=1). All the

babies were studied during the recovery phase of their illness, before weaning from respiratory support. Near-infrared spectroscopy (NIRS) was used to measure cerebral blood volume (CBV) for about 2 minutes before and after a change in ventilation. NIRS detects changes in the oxygenated and deoxygenated haemoglobin (HbO_2 and Hb) concentrations using light absorption, allowing CBV to be calculated from the total haemoglobin (sum of HbO_2 and Hb). The sequence of ventilatory changes in the IPPV group was from IPPV to endotracheal CPAP, and then back to IPPV; in the CNEP group it was from CNEP to no ventilatory support, then back to CNEP. The study design and results are summarised diagrammatically in Figure 4. The authors found a median increase in cerebral blood volume (CBV) of 0.055 ml/ 100 ml brain (95% C.I. 0.010 -0.115) on switching from IPPV to ET CPAP and a corresponding decrease of 0.045 ml/ 100 ml brain (95% CI. 0.010 -0.100) on switching back again. The changes in CBV were not accounted for by changes in arterial $paCO_2$ in the 8 studies in which it was monitored. Stopping CNEP was associated with a median increase in CBV of 0.2 ml/ 100 ml brain (95% C.I. 0.012 - 0.316) whilst restarting it brought a reduction in median CBV of 0.14 ml/ 100 ml brain (95% C.I. 0.035 - 0.280). Both ventilatory modes resulted in a reduction in CBV but CNEP was associated with a reduction in both HbO_2 and Hb whilst IPPV was associated with a reduction in HbO_2 and an increase in Hb. The authors suggest that CNEP reduces CBV by an overall effect of increased cerebral venous drainage. Conversely, IPPV would be expected to *increase* CBV by impairing venous drainage,

therefore the *reduced* CBV observed in the IPPV infants was postulated to be the result of a greater effect of IPPV in reducing cerebral arterial blood flow than in reducing venous drainage (Palmer et al., 1995).

Figure 4: Diagrammatic representation of study design and results (Palmer et al., 1995)



Raine et al., (1994) examined cerebral blood flow velocity in a pilot study of 8 preterm babies receiving IPPV and CNEP for RDS. Using the Doppler technique they found no change in the middle cerebral artery flow after stopping CNEP and maintaining equivalent settings of PEEP or on switching back to CNEP. Removal of the neck seal also had no effect on middle cerebral artery flow suggesting it did not obstruct venous return (Raine et al., 1994). In a study of 10 preterm babies receiving CNEP for RDS, Palmer et al. (1994) similarly found that removal of the latex neck seal caused no significant change in cerebral blood volume measured by near- infrared spectroscopy. There was, however, an increase in cerebral volume when CNEP was stopped, consistent with the results of the same investigators' later

study (described above), which found that CNEP enhanced cerebral venous drainage in the babies studied (Palmer et al., 1995). Tables 6 and 7 are summaries of the studies reporting outcome or physiological effects of CNEP.

1.4.4 Outcome following Negative Pressure Ventilation

1.4.4.1 Respiratory distress syndrome (short-term outcome)

Fanaroff et al. (1973) conducted the first controlled trial of CNEP versus oxygen therapy alone for the management of neonatal respiratory distress syndrome (RDS). Preterm infants (< 37 weeks gestational age) with clinical, radiological and blood gas findings consistent with RDS were recruited if they were unable to maintain arterial oxygen tension ≥ 60 mm Hg despite an inspired oxygen concentration (FiO_2) of 70%. Fifteen infants were randomly assigned to receive CNEP and 14 received oxygen therapy alone (control group). Accepted criteria for the initiation of mechanical ventilation at the time of the study were used to define 'study failures' i.e. inability to maintain $PaO_2 \geq 50$ mm Hg despite FiO_2 of 100%, or the onset of apnoea. Study failure occurred in 5 of 15 infants (33%) treated with CNEP compared with 12 of 14 infants (86%) in the control group; $p<0.05$. The 5 study failures in the CNEP group required intubation and IPPV and 11 (79%) of the 12 control failures required intubation (3 CPAP, 8 IPPV). One of the control failures was successfully managed with CNEP alone. The mean duration spent needing $FiO_2 \geq 70\%$ was significantly shorter in

the CNEP group than in controls (41.5 hrs [SD 38.3] compared to 107.4 hours [SD 85.6]; p<0.02). There was no significant difference in mortality between the groups (4 died in the CNEP group and 6 died in the control group). This study showed that CNEP improved oxygenation and significantly reduced duration of exposure to high oxygen concentration in preterm infants with RDS; its use was also associated with a significantly lower rate of intubation.

A later study by Alexander et al. (1979) compared the use of CNEP and nasal CPAP in preterm infants with RDS. Thirty-six preterm infants with clinical, radiological and blood gas evidence of RDS were recruited into a comparative study of CNEP versus nasal CPAP. Eighteen infants were randomised to each group and treated with pressures of 6 to 8 cm H_2O (CPAP) or -6 to -8 cm H_2O (CNEP) when FiO_2 > 45% was needed to maintain PaO_2 between 50 -80 mm Hg. Both methods were effective in improving oxygenation with no significant differences between groups in the PaO_2 at 30 minutes or 2 hours of treatment [CNEP Group: baseline PaO_2 52 mm Hg (SD 3.6); at 30 mins 91 mm Hg (SD 8.4), CPAP: baseline PaO_2 50 mm Hg (SD 2.9) at 30 mins 74 mm Hg (SD 6.5). The mean FiO_2 was not significantly different between the groups during the first 24 hours of treatment and decreased from about 60% to 40% in both groups. The number of hours infants received FiO_2 > 40% was also not significantly different between the groups. Four patients in the CNEP group and 7 in the CPAP group showed progressive deterioration requiring intubation and IPPV. Infants in the

CPAP group who 'failed treatment' deteriorated faster and then required assisted ventilation for longer than the failures from the CNEP group. The total time that respiratory support was required in the two groups was not significantly different. The authors found that both treatment methods improved oxygenation in preterm infants with RDS. They observed, however, that nasal CPAP was easier to administer and allowed easier access to patients but noted the smaller overall increase in PaO_2 in the CPAP group, probably because the intended pressures could not be maintained when babies cried or opened their mouths.

An abstract report by Monin et al. (1976) describes the findings of a controlled study in which intermittent negative pressure (NPV) ventilation was compared with intermittent positive pressure (IPPV) in 115 babies with RDS (57 received NPV and 58 IPPV). Birth weight, gestational age and illness severity were reported to be comparable in the 2 groups although data are not provided. The duration of oxygen therapy was the same in both groups and there was no difference in the incidence of patent ductus arteriosus, intracranial haemorrhage or mortality. A significantly lower incidence of pneumothoraces (17% versus 36%; $p< 0.05$) and radiologically diagnosed broncho-pulmonary dysplasia (5% versus 24%; $p< 0.01$) were reported in the babies treated with negative pressure.

The advances made with non-invasive/ invasive positive pressure ventilation were such that by the end of the 1970s, negative pressure ventilation was largely superseded. However, following technical improvements to negative pressure ventilators some investigators have reassessed this mode of ventilation, particularly because of concerns about the increasing incidence of neonatal chronic lung disease and the possible lower incidence of bronchopulmonary dysplasia in babies treated with NPV compared to IPPV (Monin et al., 1976). It is plausible that negative pressure ventilators have a beneficial effect on chronic lung disease because they avoid some of the negative effects of intubation like interruption to physiological mechanisms such as the 'mucociliary escalator'.

In 1996, a two-centre randomised controlled trial evaluated the use of CNEP in 244 preterm infants with respiratory distress syndrome (Samuels et al., 1996). Patients were randomised to receive standard neonatal care or standard care plus CNEP at 4 hours of age. The primary outcome measure was a clinical score, calculated at 56 days, which included measures for mortality, respiratory outcome and the presence of other neonatal complications such as cranial ultrasound abnormalities, patent ductus arteriosus and necrotising enterocolitis. Individual components of the primary outcome score were evaluated as secondary outcome measures. The primary outcome score showed an overall benefit of CNEP. The mean duration of oxygen therapy was

significantly lower in the infants treated with CNEP (18.3 days versus 33.6 days, mean difference -15.3 days 95% C.I. -30.4 to -0.2) with significantly fewer premature infants (< 36 weeks) requiring supplementary oxygen at 36 weeks post-conceptional age (11 [13%] versus 24 [26%], mean difference -13%, 95% C.I. -24 to -2). Five percent fewer infants in the CNEP group required intubation (95% C.I. 0-10). There were 28 deaths (23%) in the CNEP group and 22 deaths (18%) in the standard group; mean difference 5% (95% C.I. -3 to 14). Cranial ultrasound abnormalities were identified in 15 babies (12%) in the CNEP group and in 10 babies (8%) in the standard group; mean difference 4% (95% C.I. -4 to 12). The higher number of deaths and cranial ultrasound abnormalities in the CNEP group led to public concern about its safety; this was in spite of the lack of significance in the difference between the groups in both measures. The use of a non-validated clinical score as the primary outcome measure in the study has been criticised although the authors argue that it provided an ethical strategy to terminate the trial early if the use of CNEP was associated with significant benefit or harm. A significant limitation of the study, acknowledged by the authors, was the lack of planned long-term neurodevelopmental follow-up.

1.4.4.2 Respiratory distress syndrome (long-term outcome)

Infants enrolled in the randomised trial of the use of CNEP for neonatal RDS (Samuels et al., 1996) have been re-evaluated in a study of long-

term outcome, 9-15 years after their treatment (Telford et al., 2006, Telford et al., 2007). In the original trial, 259 children were randomised to receive standard care or standard care + CNEP; following exclusions 244 children remained paired at the end of the study. Telford and colleagues were able to trace 198 of the 205 survivors of the original cohort (54 having died in the neonatal period or later) and 133 (65% of the survivors) consented to participate in the follow-up study (Telford et al., 2006). None of the follow-up authors had been involved in the original trial and all were blinded to the subjects' original treatment. The primary outcome measure was death or severe disability and data to evaluate this were available for 187 of the original 259 children, including 65 of the original 122 pairs. There was no difference in death or severe disability between the CNEP group and controls in either paired (odds ratio for CNEP group 1.0; 95% C.I. 0.41 to 2.41) or unpaired analysis (odds ratio for CNEP group 1.05; 95% C.I. 0.54 to 2.06). Secondary outcome measures assessed included behaviour, cognitive and neuropsychological function and health related quality of life. There was no significant difference in full IQ between the two groups - however mean performance IQ, language and visuospatial performance subscores of the neuropsychological tests were all significantly higher in the CNEP group whilst behaviour scores and health related quality of life assessed using the Health Utilities Index were not significantly different between the groups. The findings of this study suggest that the use of CNEP in treating neonatal RDS is not

associated with an increased risk of later disability or psychological problems.

The same survivor group was assessed for the effects of CNEP on respiratory outcome in late childhood (Telford et al., 2007). In the original trial the use of CNEP was associated with a shorter duration of oxygen therapy and a significantly lower incidence of chronic lung disease, which might lead one to speculate as to whether it could have beneficial effects persisting into late childhood (Samuels et al., 1996). Telford et al. (2007) assessed mean airway resistance (measured with an interrupter device), spirometric measurements and the prevalence of respiratory symptoms as secondary outcome measures in the 133 survivors who consented to follow-up. No significant difference was found in any of these measures between the group treated with CNEP and controls managed with standard care.

1.4.4.3 Pulmonary hypertension

Cvetnic et al. (1990) reported an uncontrolled trial in which CNEP was used as an adjunct to IPPV for 50 babies with RDS, pulmonary interstitial emphysema (PIE) or pulmonary hypertension. Those with pulmonary hypertension were sub-divided according to whether they had meconium aspiration syndrome (MAS) or some other cause (non-MAS) making four groups for evaluation. Pulmonary hypertension was diagnosed by demonstrating right to left shunting at atrial level using echocardiography to visualise peripherally-injected saline shunting

across the foramen ovale; and by the finding of a difference in PaO_2 > 20 mm Hg in umbilical arterial blood compared to a simultaneously drawn radial artery sample. The response to CNEP was a rapid improvement in oxygenation in all groups, most marked in babies with non-MAS pulmonary hypertension whose mean PaO_2 was 30 mm Hg before CNEP, rising to 140 mm Hg within 30 minutes of starting it. The authors found CNEP to be more effective than the equivalent amount of PEEP in improving PaO_2 and were able to lower peak airway pressures in all groups to less than 50% of pre CNEP values by 12 hours. Ten infants had intraventricular haemorrhage (IVH) before starting CNEP and 4 infants in the PIE group had significant extension of their IVH while receiving CNEP ($p<0.01$). In view or this, the authors cautioned that perhaps CNEP should not be used in babies at highest risk of IVH - but they also noted that the incidence of IVH after treatment with CNEP was no different from that in other babies in their unit needing maximal ventilatory support.

In a later prospective randomised crossover study of 30 babies, Cvetnic and co-workers evaluated the use of CNEP as rescue treatment for severe hypoxaemia (Cvetnic et al., 1992). The study included 23 babies who met the criteria for extracorporeal membrane oxygenation (ECMO). Babies of 30-42 weeks gestation were recruited to the study if they needed intubation and PPV for hypoxaemia and if arterial PaO_2 remained < 45 mm Hg for at least 2 hours despite 100%

oxygen and minimum mean airway pressures of 12-15 cm H_2O (minimum values varied dependant on birth weight). The diagnoses of babies recruited included RDS, pneumonia and pulmonary hypertension due to meconium aspiration (MAS) or other causes (non-MAS). Thirty babies were randomly assigned to either CNEP or PEEP and were crossed over to the other mode of support if PaO_2 remained < 45 mm Hg after at least 2 hours of the initial treatment or an air leak developed. CNEP was substituted for the numerically equivalent amounts of PEEP whilst maintaining positive pressure ventilation in both groups of babies. Fifteen babies were initially randomised to receive PPV + PEEP and 15 to PPV + CNEP; mean time of randomisation was 23.5 +/- 19.1 hours. Two babies (13%) in the CNEP group crossed over to receive PEEP and 11 babies (73%) crossed over from PEEP to CNEP (p=0.003). Of five babies who died, 4 were originally assigned to receive PEEP; 2 of these died within 12 hours of randomisation without undergoing crossover, the other 2 babies died after crossover to CNEP. In the subset of 23 babies who met criteria for ECMO at the time of initial randomisation (11 PEEP, 12 CNEP), 1 (8.3%) crossed over from CNEP to PEEP, 9 (81.8%) from PEEP to CNEP and just 3 (13.3%) babies were referred for ECMO. Thirty-six hours into the trial, only 5 of the original 30 babies remained in the PEEP group compared to 20 in the CNEP group. CNEP was associated with a significantly higher increase in PaO_2 (69 $\pm$ 17 mm Hg versus 48 $\pm$ 27 mm Hg, $p < 0.05$) and in the arteriolar-alveolar (a/A) ratio of oxygen (0.098 $\pm$ 0.070 versus 0.078 $\pm$ 0.049, $p < 0.05$) 30

minutes after randomisation compared to PEEP. PaO_2 and a/A ratio of O_2 also increased significantly in those who crossed over from PEEP to CNEP (37 $\pm$ 5 mm Hg and 0.058 $\pm$ 0.009 versus 60 $\pm$ 12 mm Hg and 0.154 $\pm$ 0.096, $p < 0.05$). There was no significant increase in PaO_2 or a/A ratio following crossover from CNEP to PEEP (n=2). This study confirmed the groups earlier finding (Cvetnic et al., 1990) that CNEP was more effective than equivalent amounts of PEEP at improving oxygenation. It also showed that CNEP used as an adjunct to IMV was effective in severely hypoxic neonates and reduced the need for ECMO in this population. The authors surmised that CNEP may be more effective than equivalent amounts of PEEP by permitting more uniform alveolar recruitment.

1.4.4.4 Post cardiac surgery

The haemodynamic benefits of cuirass-type NPV after cardiac surgery have been reported in studies by Shekerdemian et al. (1997) and Shekerdemian et al. (1999). NPV has also been used as respiratory support in patients with phrenic nerve palsy after cardiac surgery. Raine et al. (1992) conducted an uncontrolled trial in 14 patients aged 1 week to 30 months with phrenic nerve palsy (bilateral in 4). One patient with bilateral nerve palsy and 4 with unilateral palsy had undergone diaphragmatic plication. All patients needed supplementary oxygen and 10 were receiving positive pressure ventilation before starting negative pressure ventilation. NPV was introduced in

spontaneously breathing patients with a persistent or increasing oxygen requirement and respiratory distress, and gradually substituted in those already having PPV. After initiation of NPV, 3 patients required diaphragmatic plication or re-plication and 3 died from non-respiratory causes including candida sepsis, intro-operatively during pulmonary artery banding and following a cardiac arrhythmia. Eleven patients survived after receiving NPV for 3 -241 days. At follow-up 2 - 22 months later, all surviving patients were reported to have 'normal respiratory function' although no details are provided. The authors suggest that the use of NPV may have avoided plication or re-plication in 11 patients. This study suggests that NPV can usefully support patients with phrenic nerve palsy but a controlled trial is needed to test whether it has clear benefits over positive pressure ventilation in this disorder.

1.4.4.5 Cystic fibrosis

A case report of the use CNEP in 3 infants with cystic fibrosis found it was well tolerated and associated with clinical improvement (Klonin et al., 2000). One child received CNEP at home for several months. Non-invasive respiratory support is preferable to intubation and IPPV in children with cystic fibrosis because clearance of airway secretions, of particular importance in this condition, is even more difficult after intubation. There are no controlled trials of the use of NPV for cystic fibrosis.

1.4.4.6 Congenital diaphragmatic hernia

Baglaj et al. (1998) reported an uncontrolled study of the use of CNEP in the management of babies after repair of congenital diaphragmatic hernia (CDH). Between 1981 and1995, 108 babies with CDH presented to the South West Regional Paediatric Surgical Unit in Bristol, UK. Fourteen died without surgery, as their condition could not be stabilised sufficiently. After 1990, CNEP was used as an adjunct to PPV in babies with CDH needing ventilatory support for more than 7 days post-operatively. In the 9 years before the introduction of CNEP, 17 babies were ventilated for more than 7 days; of these, 7 developed chronic lung disease and 6 died after 4 weeks, 5 from the chronic lung disease. Between 1990 -1995, CNEP was used in 11 out of 18 babies who were ventilated for longer than 7 days; there were no cases of chronic lung disease and just one late death in a child who received prolonged ECMO out of region. This study suggests that the use of CNEP may reduce the risk of developing chronic lung disease in babies requiring prolonged respiratory support; however, there are no controlled trials of the use of CNEP for CDH.

1.4.4.7 Central hypoventilation syndrome

Hartmann et al. (1994a) reported their use of CNEP in an uncontrolled trial in 9 children with central hypoventilation syndrome (CHS). The children were aged 22 days to 4 years 9 months at the onset of

treatment. With the introduction of CNEP, 7 children (78%) were successfully weaned from PPV and managed at home by their parents without the need for tracheostomy. Due to problems with upper airway obstruction, 3 needed CPAP in addition to NPV (2 for up to 2 weeks and 1 permanently). Two of the 7 patients treated with NPV were eventually weaned off all ventilatory support. Two of the original 9 could not be managed with NPV and required tracheostomy. The findings suggest that NPV may give useful non-invasive support to a majority of children with CHS but a controlled trial is needed to evaluate more fully its role in managing this condition.

Table 6: Studies of the physiological effects of continuous negative extrathoracic pressure

First author (Year)	Study group	Study protocol	Findings	Comments
Gappa et al. (1994)	18 infants, aged 10 -127 days, gestational age 24- 36 weeks with RDS	Respiratory mechanics measured in atmospheric pressure and following the application of -6 cm H_2O CNEP	CNEP resulted in a significant decrease in respiratory rate, increased compliance measured with the single breath technique but no change in respiratory resistance.	Benefits of CNEP may be explained by its effect on respiratory mechanics
Essa et al. (1994)	13 newborn piglets with induced lung injury following saline lavage	Piglets were randomly assigned to receive PEEP or CNEP at equivalent pressures of 3, 6, 9 and 12cm H_2O	No difference in lung compliance, resistance, arterial oxygen pressure or cardiac output. Lower end expiratory lung volume in the PEEP group	CNEP and PEEP may be physiologically equivalent
Raine et al. (1994)	8 babies aged 2-15 days, gestational age 25-36 weeks with RDS	All babies received both CNEP and IPPV initially; blood flow velocity was measured whilst receiving CNEP and repeated after discontinuation of CNEP.	No significant changes noted in cerebral blood flow velocity, heart rate, oxygen saturations and transcutaneous pCO_2.	No adverse effect of CNEP on cerebral blood flow velocity demonstrated
Palmer et al. (1994)	10 infants, aged 3-62 days, gestational age 27-36 weeks with RDS	Cerebral blood volume measured with near infrared spectroscopy before and after discontinuation of CNEP and during removal of neck seal	Cerebral blood volume increased significantly on discontinuation of CNEP but there was no significant change on removal of the neck seal	CNEP may enhance cerebral venous drainage; no evidence of an effect by the neck seal

First author (Year)	Study group	Study protocol	Findings	Comments
Palmer et al. (1995)	29 infants (12-CNEP 17-IPPV) aged 1-65 days, gestational age 26-37 weeks with RDS	Cerebral blood volume measured with near infrared spectroscopy whilst receiving CNEP or IPPV, following discontinuation and after resumption of CNEP or IPPV	The use of CNEP was associated with a median decrease in blood volume of 0.14ml/100ml brain (95% C.I. 0.035-0.280) compared with no respiratory support and IPPV with a median decrease of 0.06ml/10ml brain (95% C.I. 0.010-0.115). Both oxygenated and deoxygenated Hb decreased in CNEP infants, deoxygenated Hb increased and deoxygenated Hb decreased in IPPV group	Both CNEP and IPPV reduce cerebral blood flow velocity but CNEP probably causes increased cerebral venous drainage whilst IPPV reduces cerebral venous drainage but other factors may also be significant
Shekerdemian et al. (1997)	9 children, median age 6.3 years (post fontan's procedure) 9 children, median age 5.8 years (during cardiac catheterisation 5 mths-15 yrs later)	Pulmonary blood flow measured by the 'Flick method' during IPPV and NPV	Pulmonary blood flow increased during NPV from 2.3±1.2 to 3.3± 1.9 $L \cdot min^{-1} \cdot m^{-2}$ (p=0.01) in acute patients and from 2.6±1.0 to 3.7±1.1 $L \cdot min^{-1} \cdot m^{-2}$ (p=0.01) in convalescent patients.	Cuirass type negative pressure ventilation significantly increases pulmonary blood flow in children with a 'Fontan circulation'
Shekerdemian et al. (1999)	23 children aged 0.5-13years, post tetralogy of fallot repair	Pulmonary blood flow measured by the 'Flick method' during IPPV and NPV, 4-18 hours after tetralogy of fallot repair	NPV increased pulmonary blood flow by 39% after 15 minutes and by 67% after 45 minutes. Increase most marked if restrictive right ventricular physiology (84%)	Cuirass type negative pressure ventilation improves the pulmonary blood flow of patients after tetralogy of fallot repair

Table 7: Summary of studies reporting outcome following the use of continuous negative extrathoracic pressure

First author (Year)	Number of subjects	Age at follow up	Condition treated	Type of study	Findings
Fanaroff et al. (1973)	15 CNEP 14 Controls	Newborns	Respiratory distress syndrome	Controlled	67% of CNEP vs 14% of controls improved without further need for respiratory support
Monin et al. (1976)	57 CNEP 58 IPPV	Newborns	Respiratory distress syndrome	Controlled (abstract)	Reduced BPD & pneumothoraces with CNEP
Alexander et al. (1979)	18 CNEP 18 CPAP	Newborns	Respiratory distress syndrome	Randomised controlled	No significant difference
Samuels and Southall (1989)	88	1 day - 2 years	Respiratory failure	Uncontrolled	Reduced FiO_2 after 2 hrs and 48 hrs of CNEP
Cvetnic et al. (1990)	37	Newborns	Pulmonary hypertension	Uncontrolled	Rapid improvement in oxygenation following CNEP
Cvetnic et al. (1992)	30	Newborns	Pulmonary hypertension	Randomised controlled crossover	2 'CNEP' babies crossed over to PEEP, 11 'PEEP' babies crossed over to CNEP
Raine et al. (1992)	14	1 wk -30 months	Phrenic nerve palsy	Uncontrolled	CNEP used to aid weaning from PPV
Hartmann et al. (1994a)	9	22 days - 4.75 yrs	Central hypoventilation syndrome	Uncontrolled	Effective long term respiratory support

First author (Year)	Number of subjects	Age at follow up	Condition treated	Type of study	Findings
Hartmann et al. (1994b)	15 CNEP 18 Controls	40 -61 weeks post conceptual age	Bronchiolitis	Randomised controlled (abstract)	4 in the CNEP group had reduced FIO_2 to ≤30% within 1 hour compared to no controls. I control needed IPPV and another CPAP
Samuels et al. (1996)	244	Newborns	Respiratory distress syndrome	Randomised controlled	5% less intubations with CNEP, shorter duration of oxygen therapy
Linney et al. (1997)	56	13 -325 days	Bronchiolitis	Retrospective review (abstract)	Reduced intubation with CNEP
Baglaj et al. (1998)	108	Newborns	Congenital diaphragmatic hernia	Retrospective review	Reduced chronic lung disease
Klonin et al. (2000)	3	4-8 months	Cystic fibrosis	Case reports	May be useful respiratory support
Al-balkhi et al. (2005)	31 NPV, 21 controls	-	Bronchiolitis related apnoea	Retrospective review	Reduced intubation and shorter PICU stay in NPV group
Telford et al. (2006)	187	9 -15 years	Respiratory distress syndrome (Long term outcome)	Randomised controlled	No difference in death or severe disability
Telford et al. (2007)	187	9 -15 years	Respiratory distress syndrome (Long term outcome)	Randomised controlled	No difference in respiratory symptoms or respiratory function

1.4.5 Advantages and disadvantages of negative pressure support

There are several advantages of negative pressure ventilation (both continuous and intermittent negative extrathoracic pressure) over positive pressure ventilation and a similar number of disadvantages that are summarised in Table 8. When CNEP is compared with nasal CPAP, however, there are fewer advantages to its use. It is relatively more difficult to deliver and access to patients is much more restricted. There is limited evidence though that CNEP may be more effective than equivalent levels of CPAP at improving oxygenation (Alexander et al., 1979). The option of using intermittent negative pressure support in addition to CNEP, make NPV a more effective mode of ventilatory support than CPAP alone. However, non-invasive positive pressure ventilation has become possible in recent years and is increasingly being used in paediatric intensive care units (Essouri et al., 2006). When the cuirass type device is used NPV has the advantage of improving venous return and stroke volume which may be especially beneficial in some cardiac patients.

The use of CPAP in combination with NPV has been reported to be effective in overcoming the problems with upper airway obstruction which occasionally complicates the use of NPV alone (Hartmann et al., 1994a). The combination of CNEP and IPPV may have significant advantages over IPPV alone. Because the equivalent amount of CNEP may be more effective than PEEP (Cvetnic et al., 1992), the use of

both ventilatory strategies together may offer the benefits of effective ventilatory support whilst minimising ventilator associated lung injury by using a lower peak inspiratory pressure. Another potential use of NPV in combination with IPPV is to facilitate weaning from positive pressure support in intubated patients (Corrado et al., 1996).

Table 8: Summary of advantages and disadvantages of NPV (Corrado et al., 1996, Samuels and Boit, 2007)

Benefits of NPV over IPPV	Problems associated with NPV
Avoidance of intubation	Unprotected airway
Better airway clearance - physiological cough; airway suctioning without interruption of ventilation	NPV may be associated with upper airway obstruction because of constriction by the neck seal
Less likely to cause chronic lung disease	Less effective than IPPV in severe cases
Haemodynamic benefits with cuirass devices	Limited access to patients and increased nursing care

1.5 Summary of the literature

Several studies have reported long-term outcome following bronchiolitis with particular reference to its association with reactive airway disease. There remains uncertainty as to whether host responses or the effect of the infecting organism (i.e. RSV) is the reason for this association. Most studies following up children after bronchiolitis have used spirometry to assess lung function but a few have also assessed lung volumes and airway resistance by plethysmography. Two studies have been identified which provide limited data on neurological outcome following mechanical ventilation in children, including a small number

with bronchiolitis. Short-term outcome has been reported after the use of CNEP in infants with several conditions including neonatal respiratory distress syndrome, pulmonary hypertension, central hypoventilation syndrome, cystic fibrosis, congenital diaphragmatic hernia, and after cardiac surgery (including some with the complication of phrenic nerve palsy). Data on the use of NPV in bronchiolitis are provided by just four studies, one an uncontrolled study including a small number of children with bronchiolitis and 2 that were reported in abstract form only. There is no published study of long-term outcome following the use of CNEP for bronchiolitis. The following questions about the use of CNEP in bronchiolitis need to be addressed:

1. What are the short-term respiratory effects of CNEP?

2. If CNEP is beneficial for use in bronchiolitis, is it best used as ‘rescue therapy’ or at an earlier stage to pre-empt intubation?

3. Are there long-term respiratory or neurological effects of CNEP?

Ideally, these questions would be addressed by an adequately powered, prospective, randomised controlled trial but this would be difficult to carry out in light of the adverse publicity the treatment has received in the UK. However, much valuable information can be gained by a careful evaluation of past clinical experience. This thesis reports the retrospective evaluation of respiratory and functional outcome in children who were treated for bronchiolitis with NPV and provides new evidence to help answer the third question posed above.

2 Aims and hypothesis

2.1 Study aim

Using a matched cohort design this study aims to determine whether there are respiratory or neurological sequelae to the use of CNEP for the treatment of bronchiolitis.

2.2 Primary hypothesis

The null hypothesis is that there is no difference in airway resistance measured in later childhood between children who received CNEP for bronchiolitis and matched controls.

2.3 Secondary hypotheses

a) The use of CNEP for bronchiolitis does not result in an increase in respiratory symptoms in later childhood compared with matched controls.

b) The use of CNEP during bronchiolitis is not associated with an increase in disability or worse health related quality of life among surviving children compared to controls.

c) The use of CNEP is associated with short-term benefit, such as a reduced need for intubation, when compared to controls.

2.4 Study design

This was a retrospective matched cohort study of children treated with CNEP for bronchiolitis at North Staffordshire Hospital (NSH). Matched controls were recruited from a cohort of children who were admitted to Queen's Medical Centre (QMC) with bronchiolitis during the same period as the children treated with CNEP. The two hospitals are 50 miles apart in the Midlands of England and provide tertiary paediatric intensive care to similar sized populations. A small number of children in whom CNEP was used to facilitate weaning from positive pressure ventilation were also evaluated; the outcome for these children is described separately without comparison to a control group.

3 Outcome measures

Outcome measures evaluated in the study are listed below:

1. **Primary outcome:**

    a. Airway resistance measured using the interrupter technique (*R*int)

2. **Secondary outcomes:**

    a. Other lung function tests: Percentage change *R*int , FEV_1, FVC, FEF_{25-75}, percentage change FEV_1

    b. Frequency of respiratory symptoms

    c. Need for respiratory medication

    d. Prevalence of disability

    e. Health related quality of life (Health Utility Index 3)

3. **Short term outcomes:**

    a. Length of hospital stay

    b. Length of PICU admission

    c. Duration of oxygen therapy

    d. Rates of intubation

3.1 Choice of primary outcome

An increased prevalence of respiratory symptoms is the commonest adverse outcome after bronchiolitis and so it is important to identify therapies that either worsen or ameliorate this effect. Most studies of long-term outcome following bronchiolitis have assessed the prevalence of respiratory morbidity by interview, use of questionnaires or by measuring respiratory function. Several outcome studies following bronchiolitis have used the prevalence of respiratory symptoms as the primary outcome measure (Tables 2-5). It could be argued that these are more relevant than measures of lung function, also commonly used, but their disadvantage is that they tend to be subjective and liable to bias. A study by Cane et al. (2000) found only 45% agreement between parents' (n=139) and clinicians' reports of wheeze in children attending a chest clinic and the same investigators found that parents (n=190) identified wheeze with just 59% accuracy when shown a video of different respiratory signs (Cane and McKenzie, 2001).

Lung function tests, by contrast, are arguably a more objective way of assessing the prevalence of airway disease but they may correlate poorly with the prevalence of symptoms and so be of less relevance to subjects. However, some lung function tests do correlate well with clinical symptoms. McKenzie et al. (2000) found higher baseline Rint values in children with a history of wheeze compared to healthy controls. Bronchodilator responses were also significantly higher in

those who wheezed compared to controls with a median ratio of baseline to post-bronchodilator airway resistance (BDR) of 1.4 versus 1.07. Children with chronic cough but no wheeze (presumed cough variant asthma) had an intermediate bronchodilator response ratio (BDR) of 1.27, also significantly higher than the controls.

A lung function measure was selected as the primary outcome for this study because objectivity was considered to be crucial in determining any difference between the two groups. The frequency of respiratory symptoms was assessed as a secondary outcome measure.

The measurement of airway resistance and lung volumes by plethysmography (R_{aw}) is considered to be the 'gold standard' method of assessing airway disease in children (Hammer and Eber, 2005). The technique for this involves a subject breathing against a closed valve whilst inside a perspex body box which children less than 8 years old find difficult. With sedation plethysmography can be achieved successfully even in infants (Stokes et al., 1981). It was anticipated that most subjects would have difficulty cooperating with this technique or would require sedating, posing ethical difficulties and probably also deterring parents from consenting to the study. A recent modification of the plethysmography technique involves the measurement of specific airways resistance (sR_{aw}), which avoids the need to breathe

against a closed shutter, and can be done with a parent also inside the box, both factors improving the acceptability of the procedure. However, the plethysmography box is bulky and therefore not easily transported; it is also very expensive. To avoid subjects having to travel long distances to participate in the study; and to maximise recruitment, evaluations were planned to be carried out at two centres (one in each city), close to the subjects' homes. Achieving this would have needed two plethysmography boxes and their high cost precluded this option.

Respiratory function has been assessed in most outcome studies of bronchiolitis by using spirometry. The flow volume curve produced by forced expiration is a widely used and well characterised test of respiratory function. It has the benefit of extensive normative data for both a wide age range and for different ethnic groups. With appropriate training and the use of incentive displays, some very young children can be coached to perform the test - however about half of 3 -6 year olds may not be able to do it adequately (Dundas and McKenzie, 2003). This was considered to be a significant limitation to its use as the primary outcome measure in this study. With over a third of the CNEP cohort aged 4.5 - 6 years at the time of evaluation, it was anticipated that spirometry might not be possible in about 20% of subjects.

The forced oscillation technique (FOT) and the impulse oscillation system (IOS) are two non-invasive methods that have recently been used in children and adults to assess airway resistance. They deduce the mechanical properties of the respiratory system by measuring impedance to airflow after applying externally-produced pressure waves (oscillation); resistance and reactance are then calculated from the measurements obtained (Hammer and Eber, 2005). Although this is a promising development in paediatric lung function testing, the measurements obtained using FOT are less reproducible than those from airway resistance measured with an interrupter device (*R*int) and specific airways resistance (sRaw) in children aged 4-6 years (Bisgaard and Klug, 1995, Klug and Bisgaard, 1998). They were also found to be unreliable in up to a third of 5 year olds undergoing bronchial challenge (Wilson et al., 1995). The equipment used for FOT is larger and more expensive than interrupter systems which are also easier to operate and have been standardised in children up to 13 years of age (Merkus et al., 2002, McKenzie et al., 2002).

3.2 Airway resistance - interrupter method (*R*int)

Assessment of airway resistance by the interrupter method (*R*int) involves measuring airflow and airway pressure at the mouth in tidal breathing just before and after transiently occluding the airway with a rapidly moving shutter. It is based on the assumption that transient occlusion of the airway at the mouth results in rapid equilibration of

alveolar pressure with mouth pressure. The difference between the pressure at interruption and the baseline pressure prior to interruption is thought to reflect resistance in the pulmonary airways and *R*int is the ratio of this difference in pressure to flow at the time of interruption (Bates et al., 1987, Chowienczyk et al., 1991). In the same way that alveolar pressure is not a single value, airway resistance measured by this technique represents an average resistance value of the airways.

3.2.1 History of the interrupter technique (*R*int)

The interrupter technique for measuring airway resistance was first described by Von Neergaard and Wirz (1927) but failed to gain wide acceptance for many years. The values obtained were found to differ from the 'gold standard' values of airway resistance measured by plethysmography (Raw) and physiological interpretation of the method remained unclear (Dundas and McKenzie, 2003, Bridge et al., 1996). There has been renewed interest in the technique since the late 1980s following theoretical and animal work by Bates and co-workers (Bates et al., 1987, Bates et al., 1988b, Bates et al., 1988a, Bates et al., 1989a, Bates et al., 1989b). Studies in anaesthetised open-chested dogs with tracheostomy showed *R*int to be an excellent approximation to Raw in that model (Bates et al., 1988b). In closed-chested dogs, *R*int was found to have a strong *correlation* with Raw but, by including a contribution from the chest wall, tended to exceed it (Bates et al., 1989b, Bates et al., 1989a). The authors also identified that upper

airway compliance may result in an underestimate of Raw which can be minimised by supporting the cheeks and pharynx (Bates et al., 1987). Theoretical analysis of the technique by Bates and co-workers suggests that *R*int is a valid method of assessing airway resistance (Bates et al., 1988a). Chowienczyk et al. (1991) evaluated *R*int in 43 adults with varying degrees of airflow obstruction and found a similarly good correlation with Raw (r=0.86); they also tried the technique in 10 children aged 3 years and found that they were able to use it successfully.

Since the early 1990's *R*int has gained wide use in adults and children. Its main advantage over spirometry and plethysmography is that it involves a simple technique and requires only minimal cooperation, making it suitable for use even in preschool children. Bridge and McKenzie (2000) found that, of 100 children aged 5-10 years (consecutive referrals to a tertiary respiratory centre) who were tested with both spirometry and *R*int, 97% were able to complete the *R*int test compared to 53% able to complete spirometry. *R*int has also been shown to be of value in detecting bronchodilator responsiveness, a key diagnostic criterion for asthma. In a study by McKenzie et al. (2000), a pre- to post-bronchodilator *R*int ratio of 1.22 was found to be 80% specific and 76% sensitive for previous wheeze. Bridge et al. (1996) found *R*int to be as sensitive as spirometry at detecting bronchodilator responses in a study of 25 school-aged children with asthma. Its

usefulness for comparing treatment outcomes has been demonstrated in 2 studies evaluating the effect of inhaled corticosteroids in asthmatic preschool children. A randomised placebo-controlled study of inhaled budesonide in 38 children aged 2-5 years with asthma, found significantly lower Rint values in the treatment group after 8 weeks (Nielsen and Bisgaard, 2000). Baseline *R*int and BDR were primary outcome measures in a study by Pao and McKenzie (2002) in which they evaluated the use of inhaled fluticasone in a randomised placebo-controlled crossover trial in 61 children aged 2-5 years with asthma. After 6 weeks treatment *R*int was 7.6% lower than baseline in the group as a whole and 16% lower in 14 children who were skin prick test positive to one or more of the common aeroallergens. Similarly the BDR fell by 5.6% overall after 6 weeks of inhaled fluticasone and by 10.6% in skin prick positive subjects. *R*int values returned to baseline 16 weeks after stopping treatment.

3.2.2 Technical aspects of performing *R*int

Bates and co-workers showed that *R*int values are an approximation of airways resistance. The flow just prior to interruption and the pressure change following interruption are both measured at the mouth and used to calculate airway resistance. The technique is based on the assumptions that the shutter closes instantaneously and is followed by an instantaneous equilibration of airway opening pressure with alveolar pressure. The exact pressure at interruption is obscured by a series of

oscillations, caused by the inertia of gas in the airway and compliance of the airway walls. A back-extrapolation method is most commonly used to estimate the alveolar pressure at the point of interruption. Several methods of analysing the mouth pressure/time curve to determine *R*int have been evaluated including a measurement of the pressure change after the post interruption oscillations have decayed or the pressure change at the end of the period of interruption (Phagoo et al., 1995). The two-point linear back extrapolation method for calculating *R*int resulted in the lowest baseline variability and was the most sensitive at detecting change following methacholine challenge when compared with other methods (Phagoo et al., 1995). It has been proposed as the accepted standard (Carter, 1997) and is currently the most widely used.

To perform a *R*int measurement, the subject is asked to take normal tidal breaths through a mouthpiece attached to the interrupter device (Figure 5). Closure of the valve is actuated when airflow reaches a predetermined value and takes about 5 milliseconds (ms) (Chowienczyk et al., 1991). During the process of closure, some gas continues to flow through the valve so lung volume and alveolar pressure continues to change (Bates et al., 1987). The changes in volume and pressure that occur during the time it takes for valve closure have been found to be of little clinical importance provided complete occlusion occurs within 10 -20 ms (Sly and Lombardi, 2003).

The valve remains closed for about 100 ms during which pressure is measured at 1ms intervals and the results stored in the computer memory (Chowienczyk et al., 1991)

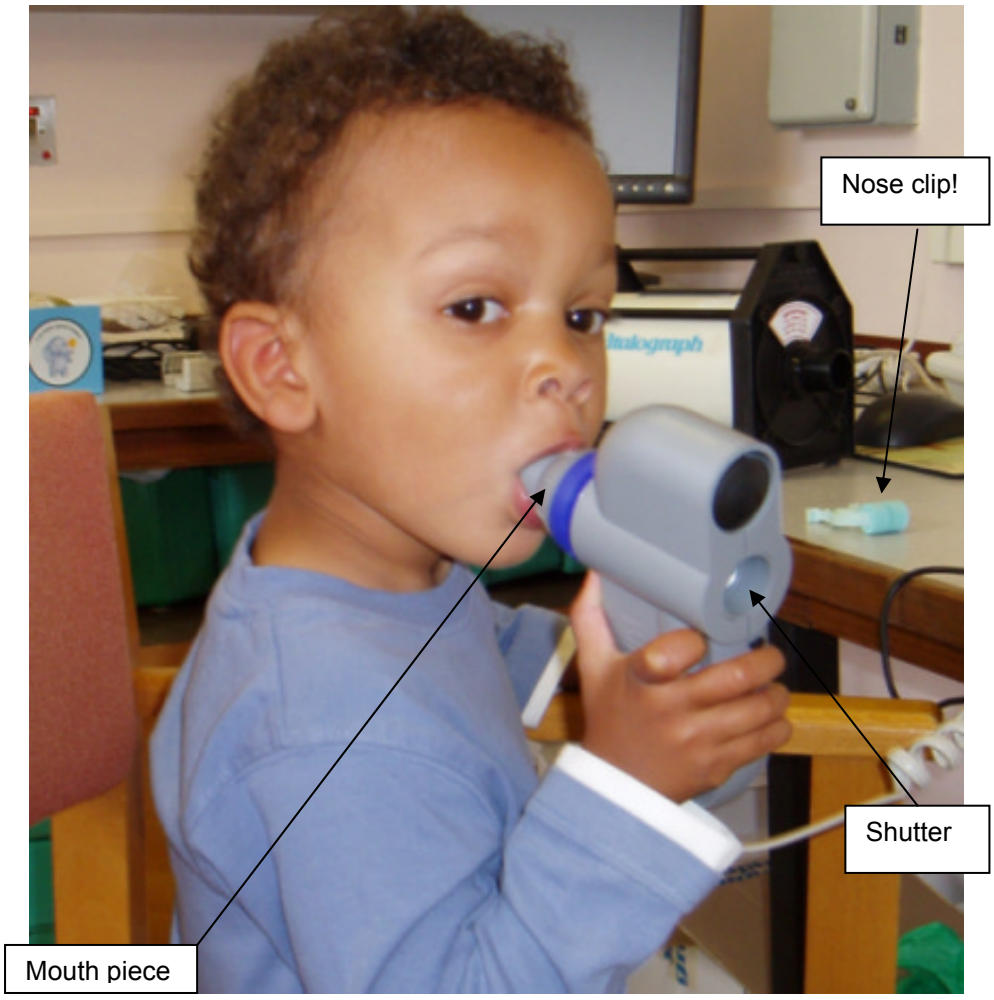


Figure 5: A child aged 2 years and 10 months holding a Micro-Rint^{TM} device

Factors that can affect its measurement include air leak around the mouthpiece, compliance of the cheeks, neck position, airflow rate and lung volume at interruption. The results obtained are also affected by both the type of device used and by the criteria chosen for selecting the

post-occlusion pressure (Pao et al., 2004). All these factors may significantly affect the result of a single *R*int measurement (Phagoo et al., 1996) but reliability of results can be improved by standardising technique in the following ways:

1. The two-point linear back extrapolation method for calculating airway resistance has been shown to have the least baseline variability and the highest sensitivity for detecting a response to inhaled methacholine when compared with other methods (Phagoo et al., 1995).

2. Measurements taken in expiration are more sensitive at detecting differences in airway calibre than in inspiration (Merkus et al., 2001).

3. Upper airway compliance can be minimised by supporting the cheeks and pharynx during testing (Bates et al., 1987).

4. Taking the median of at least six readings significantly increases reliability of results (Bridge and McKenzie, 2001).

Figure 6 is an example of a typical pressure-time curve produced as a result of airway occlusion during the measurement of *R*int.

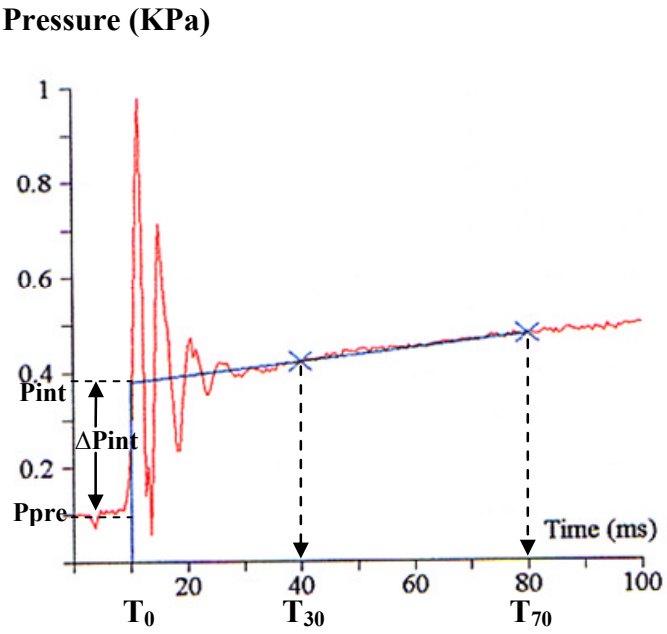


Figure 6: Mouth Pressure-time curve showing back extrapolation of Rint

P_{pre} is the mouth pressure measured prior to occlusion, during tidal breathing. Valve closure during expiration results in a sharp increase in pressure within the mouth, a series of high-frequency oscillations and then a smooth increase in pressure. The time of airway occlusion (T_0) is defined as the point at which 25% of the peak value of the first pressure upstroke is reached. The airway pressure at T_0 is obtained by linear back extrapolation using 2 points from the curve at 30 and 70 ms post occlusion (T_{30} and T_{70}). Mouth pressures pre occlusion (P_{pre}) and at time T_0 (P_{int}) are used in the later calculations. The pressure at interruption (P_{int}) is an approximation of alveolar pressure and airway resistance (*R*int) is determined by the ratio of ΔP_{int} (the difference

between P_{pre} and P_{int}) to the expiratory flow at the mouth immediately before interruption (Chowienczyk et al., 1991, Phagoo et al., 1996).

3.2.3 Summary of *R*int

The main advantage of *R*int over other methods of assessing airway resistance is the ease with which it can be performed, allowing its use in preschool children. It is portable, affordable and reproducible results can be obtained by relatively inexperienced personnel (Phagoo et al., 1996). Several studies have found good correlation between *R*int values and airways resistance obtained by plethysmography (Raw) in both normal and asthmatic children (Merkus et al., 2001, Carter et al., 1994, Chowienczyk et al., 1991) and there is good correlation between *R*int and spirometric measurements such as PEF and FEV_1 (Carter et al., 1994). The reported 'within-occasion' reproducibility of *R*int is varied with some studies suggesting it is satisfactory and similar to R_{aw} (Oswald-Mammosser et al., 1997, Merkus et al., 2001), whilst other studies suggest a high coefficient of variability particularly in patients with airway obstruction (Chan et al., 2003). The 'between-occasion' variability of *R*int is high limiting its usefulness for monitoring a child's illness over time (Chan et al., 2003); an area of use where *R*int compares unfavourably with spirometry. Most lung function tests that assess airflow resistance, including *R*int, tend to underestimate airway disease in those with asthma because equilibration of mouth and alveolar pressure may occur more slowly in obstructed airways

(Bisgaard and Klug, 1995, Oswald-Mammosser et al., 2000). Despite these limitations, the interrupter technique remains useful in detecting airway disease and is particularly sensitive at determining a bronchodilator response (McKenzie et al., 2000, Bisgaard and Klug, 1995). The determination of normal values for children aged 2-13 years has further increased its usefulness (Lombardi et al., 2001, Merkus et al., 2002, McKenzie et al., 2002). *R*int was chosen as the primary outcome measure for this study because, limitations notwithstanding, it offers a practical, sensitive, validated and objective tool for comparing the two cohorts of children.

3.3 Secondary outcomes- Respiratory

3.3.1 Respiratory function tests – Spirometry/ Reversibility studies

The following respiratory function tests have been evaluated as secondary outcome measures: baseline and percentage change FEV_1, FVC, FEF_{25-75}, percentage change *R*int and *R*int bronchodilator response ratio (BDR ratio). Forced expiratory manoeuvres have been reported in several studies evaluating outcome in children following bronchiolitis (Table 5); their inclusion as outcome measures in this study allows for comparison of the findings with published data. The forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) are the 2 most commonly reported spirometric measures and provide a useful assessment of airflow obstruction or restrictive lung disease respectively. The forced mid expiratory flow (FEF_{25-75}) is

reported less often than FEV_1 and FVC but is a more sensitive marker of small airway disease than FEV_1 (Valletta et al., 1997). A minimum 12% change in FEV_1 following a bronchodilator is one of the standard criteria for diagnosing asthma (Miller et al., 2005). The *R*int bronchodilator response ratio has recently been identified as having high sensitivity and specificity for detecting children with a history of wheeze (McKenzie et al., 2000).

3.3.2 Respiratory symptoms and use of medication

A difference in the prevalence of symptoms between the groups, although potentially less objective, may arguably be of more relevance as an outcome measure than airway resistance. To improve the reliability of the data obtained, a questionnaire that has previously been validated for use in the International Study of Asthma and Allergies in childhood (ISAAC) was chosen to assess this secondary outcome measure. ISAAC is a large epidemiological study involving over 700,000 children, which was designed to investigate the prevalence of asthma in different populations worldwide (The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee, 1998). Other study aims were to obtain baseline measurement to allow assessment of future trends in the prevalence of asthma and to identify aetiological factors associated with its increasing incidence (Asher et al., 1995). Questions that make up the core questionnaire were selected because they have been shown in previous studies to detect

differences between populations and have been assessed for validity (Table 9). The validity of the questions was further evaluated in a study of 168 children with previous wheeze who completed the questionnaire prior to assessment by a respiratory physician (Jenkins et al., 1996). The children also underwent a bronchial challenge with hypertonic saline; bronchial hyper-responsiveness (BHR) was confirmed if there was as a 15% reduction in FEV_1 from baseline following inhaled saline. The physician was blinded to the subjects' questionnaire responses and bronchial challenge results and made a diagnosis of asthma based on standard clinical criteria. Using physician diagnosed asthma as the gold standard, the ISAAC questionnaire had sensitivity of 0.85 (95% C.I. 0.73-0.93) and specificity of 0.81 (95% C.I. 0.76-0.86) for detecting physician diagnosed asthma in children, with a positive predictive value of 0.61 (95% C.I. 0.5-0.71) and negative predictive value of 0.94 (95% C.I. 0.88-0.98). BHR had a much lower sensitivity for detecting physician diagnosed asthma 0.54 (95% C.I. 0.48-0.67) but was more specific 0.89 (95% C.I. 0.83-0.94). These findings suggest the ISAAC questionnaire is a valid tool to use to compare the prevalence of wheezing symptoms in the groups evaluated in this study. Data on the use of bronchodilator therapy or inhaled corticosteroids have also been collected to identify whether an increased use of medication in one group may account for any difference in the prevalence or frequency of symptoms.

Table 9: ISAAC Study Core Questionnaire – wheezing (Asher et al., 1995)

1. Have you ever had wheezing or whistling in the chest at any time in the past?
2. Have you had wheezing or whistling in the chest in the last 12 months?
3. How many attacks of wheezing have you had in the last 12 months?
4. In the last 12 months, how often on average, has your sleep been disturbed due to wheezing?
5. In the last 12 months has wheezing ever been severe enough to limit your speech to only one or two words at a time between breaths?
6. Have you ever had asthma?
7. In the last 12 months, has your chest sounded wheezy during or after exercise?
8. In the last 12 months have you had a dry cough at night apart from a cough associated with a cold or a chest infection?

3.4 Secondary outcomes- Functional

Adverse neurological outcome following bronchiolitis is rare, however two reported uncontrolled studies suggest it may occasionally occur as a consequence of circulatory failure associated with severe bronchiolitis (Bray and Morrell, 1982, Wren et al., 1982). The study by Samuels et al. (1996) evaluating the use of CNEP in preterm babies with RDS, led to concern that it might be associated with later adverse neurological outcome in some children because of a non-significant increase in cranial ultrasound abnormalities associated with its use. A few parents expressed the view that the use of CNEP had been responsible for subsequent disability in their children at the time of a government enquiry into the conduct of research at NSH (Griffiths, 2003). The study reported here is insufficiently powered to detect a small or subtle difference in neurological outcome due to the constraints of the original cohort size and the rarity of adverse

neurological outcome - a large difference, however, should be detectable and has therefore been evaluated as a secondary outcome measure.

3.4.1 Disability

In assessing the level of disability in the two cohorts of children, it was first necessary to define disability for each domain to be studied. The World Health Organisation (WHO) has established criteria for defining disability (World Health Organisation, 1980) and an adaptation of these was published by the National Perinatal Epidemiology Unit and Oxford Health Authority (1995). These more detailed criteria were originally described for assessing disability in ex-preterm children at 2 years of age but, with appropriate modifications, they have been shown to be of value in the assessment of older children (Marlow et al., 2005).

Using criteria described in the NPEU/ Oxford HA report, the categories of impaired/ mild and moderate/ severe disability have been defined for 6 domains of disability. Table 9 below lists the definitions of disability used in this study. Children were deemed to have an impairment or mild disability if they had abnormal clinical signs with normal motor function or mild clumsiness but were able to function independently; if they were receiving extra support in a mainstream school and if they had near normal hearing or vision with or without the use of aids. Disability was deemed moderate/severe if a child required aids for mobility, placement in a special needs school, persistent defects of

hearing or vision despite aids or required a high degree of supervision or dependence on their carer. Behavioural disability was determined by parent responses to the 'Strengths and Difficulties questionnaire' and the impact of any behaviour problems by the 'impact score'. Children were also specifically assessed for the presence of cerebral palsy.

3.4.1.1 Cognitive disability

An assessment of cognitive disability in children would ideally include psychometric testing by a trained psychologist. However, because cognitive disability is a rare outcome following bronchiolitis and in view of the limited power of this study to detect small differences in this outcome measure, the use of psychometric tests was considered inappropriate. Instead it was decided to simply record whether or not children had been identified at school as having special educational needs. The two categories of disability described are: (1) Impaired or mild disability – children receiving additional educational support in a mainstream school and (2) moderate or severe disability – children placed in a 'special needs school'. All children placed in 'special needs schools' will have had a 'statement of educational needs'. This involves a multi-disciplinary assessment process by the health professionals involved in the child's care and educational psychologists. Many children in mainstream school also have a 'statement of educational needs' and will be offered additional support without the need to be placed in special needs schools. Others will not have a 'Statement' but are acknowledged by their teachers to have difficulties and so receive

extra attention. Children are generally only considered for placement in special needs schools after going through the process of assessment for a ‘statement’ and if their needs cannot be met in mainstream schools. The effect of this is that children placed in special needs schools are generally those with a cognitive or learning disability more severe than children who receive additional support in a mainstream school. For this reason there is likely to be good correlation between a child’s degree of cognitive disability and the level of special educational needs they receive or type of school they attend. It is probable that some children with mild cognitive disability will not be identified using these criteria because the school will not have identified their problems. Children with significant disabilities, however, should be identified with these criteria and are arguably the group most important to identify.

3.4.1.2 Neuromotor disability

The assessment of neuromotor disability was based on a combination of the gross motor function classification system (GMFCS) (Palisano et al., 1997) and clinical examination techniques described by Amiel-Tison and Stewart (1989). The GMFCS was originally devised and validated for the assessment of children with cerebral palsy (CP) but is useful for the classification of gross motor disability of other causes. It is a five-level classification system based on a child’s usual performance in which level 1 grades the least disability and level 5 the most (Table 10).

Table 10: Gross Motor Function Classification System (Palisano et al., 1997)

Level 1	Walks without restrictions; limitations in more advanced gross motor skills -reduced speed, balance and coordination.
Level 2	Walks without assistive devices, limitations on uneven surfaces, inclines, crowds or confined spaces. Minimal ability (at best) to perform gross motor skills such as running and jumping.
Level 3	Walks with assistive mobility devices; limitations walking outdoors and in the community. Depending on upper limb function can propel a wheelchair manually or is transported when travelling for long distances or on uneven terrain outdoors. Able to sit independently.
Level 4	Self-mobility with limitations. Needs adaptive seating for head control and to maximise hand function. Walks only short distances with assistive devices. Difficulty turning. Difficulty on uneven surfaces. May rely on wheeled mobility. Self-mobility using powered wheelchair.
Level 5	No means of independent mobility or self-mobility using powered wheelchair with extensive adaptations. Lack independence even in antigravity postural control.

3.4.1.3 Behavioural disability

Behavioural disability was defined using scores generated from the strength and difficulties questionnaire (SDQ) which was completed by parents (Goodman, 1997). The SDQ is a behavioural screening questionnaire that may be completed by parents and teachers of 4 -16 year olds. A self-report version is available for children aged between 11-16 years (Goodman et al., 1998). The questionnaire has been validated for use as a screening tool in a nationwide sample of over 10,000 British children (Goodman et al., 2000). It is used to screen for behavioural symptoms in 5 different categories namely: conduct problems, hyperactivity-inattention, emotional symptoms, peer problems and prosocial behaviour. An extended version of the

questionnaire which includes an impact supplement has been found to discriminate more effectively between children with psychiatric symptoms and children with a psychiatric disorder (Goodman, 1999). Used on its own the SDQ has been shown to have a negative predictive value of about 95% but a positive predictive value of only 35% (Goodman, 2001). The sensitivity of the questionnaire is significantly improved with the use of a computer algorithm that combines responses from 'multi-informants' (parents, teachers, older children), identifying individuals with a psychiatric diagnosis with 95% specificity and 63% sensitivity (Goodman et al., 2000). Because behavioural disability was assessed as a secondary outcome measure and the testing done in a clinic setting, the increased sensitivity achieved by obtaining the teachers' responses was considered to be unnecessary. Children in the study were not old enough to complete the self-report version of the questionnaire and so parent responses to the extended questionnaire are reported.

3.4.1.4 Visual / Hearing / Other disability

The criteria for defining disability in the domains of vision, hearing and 'other disability' were selected for the same pragmatic reasons as were those for cognition. The levels of disability in each domain are defined in Table 11 and were assessed by a parent questionnaire.

Table 11: Definitions of 6 domains of disability

	Definitions	**Cognitive**	**Neuromotor**	**Vision**	**Hearing**	**Behaviour**	**Other, e.g. medical condition, communication problem**
Impairment or mild disability	*Problems in body structure or function such as significant deviation with no loss of function* ***OR*** *Some loss of function but able to function independently*	Learning difficulties requiring extra support in a mainstream school	Abnormal signs with normal function **OR** GMFCS level 1 Upper Limbs: Clumsiness of fine movements but independent	Normal or near normal vision with correction despite the presence of an eye defect	Hearing impairment not sufficient to require aids **OR** Hearing loss fully corrected with aids	SDQ: One or more abnormal sub-scores with a normal impact score on parent report	1. Medical condition that requires medication most days **OR** 2. Chronic medical condition requiring >2 admission /year, causing growth problems, or requiring special diet **OR** 3. Epilepsy with >1 generalised fit /month **OR** 4. Stoma **OR** 5. Uses sign language, communicates effectively
Moderate or severe disability	*Aids or assistance required to perform some tasks.* *Moderate difficulty in performing some activities* ***OR*** *Unable to perform activity without aids or assistance most of the time, or completely dependent upon carer*	Learning difficulties requiring placement in a special needs school	GMFCS level 2-5 Upper Limbs: Requires aids or assistance to feed and dress	Blind or impaired vision not fully corrected	Hearing loss not fully corrected with aids	SDQ: Abnormal total difficulties score with an abnormal impact score	1. Medical condition requires supervision most of the time (includes continuous home O_2) **OR** 2. Communication severely limited

GMF= Gross Motor Function, SDQ= Strengths and Difficulties Questionnaire

3.4.2 Health-related quality of life- HUI3

Most research on outcome following ventilation has focused on physiological and clinical end points such as oxygenation, extubation rates and survival. Increasingly, researchers have become interested in patient-assessed outcomes including quality of life, functional health status and symptoms. Functional health status is used to describe an individual's ability to perform tasks of daily living and may be categorised for ambulatory, manual, cognitive, hearing and visual disabilities. Although these are inherently subjective, it is argued that they are no less valid as measurable physiological outcomes are only important to patients if they affect the quality or quantity of their life (Randall Curtis, 2002).

A number of questionnaires have been devised to assess a patient's subjective experience of the effect of health and illness on their quality of life. The Health Utilities Index (HUI) is one such validated questionnaire that has been used extensively in clinical studies; the third version (HUI3) has evolved from the first and second versions and is the most detailed descriptive classification of the 3 systems (Feeny et al., 1996). The HUI has two components, a multi-attribute health status classification system that may be used to describe health status and a multi-attribute utility function that is used to value health status by way of a utility score. The utility score is computed from a mathematical formula and represents the mean community preference for a particular health status on a scale where dead =0.00 and perfect health =1.00. It

is based on preference measurements obtained from a survey of a random sample of 504 adults from Hamilton, Ontario. HUI was initially developed to evaluate outcomes in very low birth weight infants and comprised of four attributes: physical function, role function, social-emotional function and health problem. Following its inception, a core set of the most important attributes was determined and used in a second version (HUI2) to specifically assess morbidity associated with childhood cancer. HUI3 has evolved from HUI2 primarily to address concerns about the applicability of HUI2 to a general population. The attributes have been selected to be structurally independent, each contributing unique information, thus making the HUI3 classification system more efficient than the earlier versions. HUI3 has 8 attributes: Vision, Hearing, Speech, Ambulation, Dexterity, Emotion, Cognition and Pain, with 5 or 6 levels of function for each. It can be used to describe almost a million (972,000) unique health states.

The HUI3 has been shown to distinguish between health states in paediatric populations known to have clinically important differences. In a study of 156 extremely low birth weight (ELBW) survivors assessed at 8 years of age, Saigal et al. (1994) found the mean multi-attribute HUI2 score (0.82, SD 0.21) to be significantly lower than 145 normal birth weight children (0.95, SD 0.07; $p< 0.0001$) who were matched for age, sex and socio-economic status. The authors found that 50% of ELBW children had scores below 0.88 compared to 10% of the controls and only 17% of the ELBW scores were 1.00 compared with 50% of

controls. These results provide a perspective from the general population that ELBW children have an increased long-term health burden compared to the normal birth weight controls. An increased health burden was similarly identified in 126 children or young people (aged 6-21 years) with 'fetal alcohol spectrum disorder' in a prospective cross sectional study by (Stade et al., 2006). Mean HUI scores of 0.47 were measured in this group compared with a mean of 0.95 in the reference population of healthy Canadian children. The HUI was selected to assess functional health status in this study because it has been shown to be a valid tool with the ability to identify important differences in different paediatric populations.

3.5 Short-term outcomes

Most of clinical practice is about the risk-benefit ratio of treatment. It is important to ascertain whether the use of CNEP for bronchiolitis has beneficial short-term effects over conventional management; adverse long-term effects of any treatment can only be properly interpreted if the beneficial effects of the treatment are known. The published data on short-term outcome after the use of CNEP for bronchiolitis are limited so the short-term outcome findings of this study may be particularly relevant (Samuels and Southall, 1989, Hartmann et al., 1994b, Linney et al., 1997, Al-balkhi et al., 2005). The measures that could be reasonably assessed in a retrospective study such as this were: rates of intubation, length of PICU/ hospital stay and duration of oxygen therapy.

3.6 Matching

The following variables were used in the selection of matched controls:

- Sex (male/ female)
- Gestational age (<32 weeks, 32-36 weeks, >36 weeks)
- Oxygen dependency as an index of illness severity

Gestational age and sex were chosen because they are the two factors that most influence the outcomes of airway disease and disability. Airway disease is more common in ex-preterm infants (compared with those born at term) because of their increased incidence of neonatal lung disease (Korhonen et al., 2004) whilst disability has consistently been found to be more common in males (Wood et al., 2000, Kraemer, 2000). Oxygen dependency was chosen as the criterion for matching illness severity after it became clear, following a review of the medical notes of index cases, that an illness severity score could not be used.

3.7 Assessment of illness severity

Illness severity scores, used since the early 1980's, have proved to be particularly useful when assessing differences in outcome between intensive care units (Pollack et al., 1987). They were developed as probability models to predict the mortality risk in patients with serious illness requiring intensive care but have also proved useful for comparing outcomes from different units by accounting for differences in illness severity of admissions. A variety of scores have been used for different age groups and different types of intensive care provision.

Several scores have been validated for use in neonatal intensive care including Score for Neonatal Acute Physiology (SNAP) / SNAP with Perinatal Extension (SNAPE) (Richardson et al., 2001), Clinical Risk Index for Babies (CRIB) (Fowlie et al., 1998) and Neonatal Acute Physiology Parameters Index (NAPPI)(Corcoran et al., 1998). Fewer scores are validated for use in children needing paediatric intensive care; the most widely used is the Pediatric Risk of Mortality (PRISM) III score (Pollack et al., 1996), a third generation physiology-based predictor of mortality risk, which was initially derived from the Physiologic Stability Index (Pollack et al., 1987). It is based on 17 physiological variables measured 12 hours and 24 hours after admission. Other scores in common use tend to be illness-specific such as the Glasgow Meningococcal Septicaemia Prognostic Score (Riordan et al., 2002) or Clinical Asthma Score (Wood et al., 1972).

The use of such scores was considered for this study as a way of accurately matching cases and controls for illness severity. The PRISM and clinical asthma scores would have been suitable but the parameters needed to calculate them (blood gas, blood chemistry and mental status scores) were not recorded in all cases of interest. A significant proportion of children in the study were not admitted to an intensive care unit where such parameters might have been routinely recorded. Thus for pragmatic reasons the oxygen requirement just prior to ventilation (or maximum FiO_2 if not ventilated) was selected because

it was the one parameter of illness severity that was consistently recorded in all the medical notes. To further ensure appropriate matching without the option of a validated illness severity score, clinical guidelines for the assessment of illness severity in children with bronchiolitis were used (Table 12). Children were matched within categories of mild, moderate or severe illness.

Table 12: Guidelines for the clinical assessment of children with bronchiolitis (Hodge and Chetcuti, 2000)

	Mild	Moderate	Severe
SaO_2 in air	> 93%	86-92%	< 85%
Apnoea	No	No	Yes
Cyanosis	No	Yes	Yes
Recession	Mild	Moderate	Severe
Respirations/ minute	< 50	50-70	> 70
FiO_2 to keep SaO_2 >93%	Air	21% - 40%	> 40%
Heart rate/ minute	<140	140 -160	>160
Feeding	Feeding well	Not feeding	Not feeding

Two or more criteria must be met to justify a given category

4 Methods

4.1 Study Population - Index cases

CNEP was used routinely for ventilatory support of children with bronchiolitis at the NSH and no record was kept of which children received this therapy. Therefore, identification of the study population first required a detailed search of computer records and ward diaries to determine all children diagnosed with bronchiolitis during the period when CNEP was known to have been used (January 1993 - March 1999). A search was then undertaken of the medical notes of children identified with bronchiolitis in the relevant period, to determine all those who received CNEP. If evidence of CNEP use was found, details of the admission with bronchiolitis and neonatal history were recorded.

4.1.1 Computer records

Children admitted to NSH with bronchiolitis between April 1996 and March 1999 were identified using computer records; they numbered nearly 1200. It was not feasible to search this number of notes in the time available and it was decided to examine only those of children who had a hospital stay of longer than 4 days. This was based on the pragmatic assumption that children requiring CNEP would have moderate or severe bronchiolitis and so would almost certainly have stayed in hospital for longer than the median length of stay for bronchiolitis admissions, which in the UK is 4 days (Behrendt et al., 1998). In this way the number of notes to be searched was reduced to

257 from the total of 1194. Data on length of hospital stay was obtained from Patient Administration System (PAS) records.

4.1.2 Ward admission diaries

In NSH there were no computer records of admission diagnosis before April 1996 and so to identify admissions for bronchiolitis between January 1993 and April 1996 the ward diaries were used. All children with bronchiolitis who needed respiratory support were admitted to either the Paediatric Intensive Care Unit (PICU) or the children's respiratory ward, which also served as a High Dependency Unit (HDU). The diaries were searched both for children whose admission diagnosis was recorded as 'bronchiolitis' or 'RSV positive', and for those (the majority) in whom no diagnosis was stated but instead had recorded admission symptoms deemed to be suggestive of bronchiolitis (cough, wheeze, shortness of breath or 'chestiness' in infants admitted during the months of October- April i.e. the RSV bronchiolitis season). The medical notes were examined for all those children whose admission lasted more than 4 days for the reasons explained in section 4.1.1, above. The length of hospital stay was determined from the patient administration system (PAS) records of admission, which was in use from March 1994 onwards. The notes were sought for all children admitted to the PICU with a diagnosis of bronchiolitis, regardless of their length of hospital stay. All the notes

obtained were searched for evidence of treatment with CNEP during the admission with bronchiolitis.

The HDU ward admission diaries for January 1993-May 1994 could not be found. An attempt was made to identify the children admitted with bronchiolitis and treated with CNEP during this period, by searching through the diaries of the 'short-stay' ward. This was an assessment ward where children referred to hospital by family practitioners were first seen before being admitted to other wards or being discharged home again. As before, the diaries were searched for children with respiratory symptoms during the months of the RSV season (October-April). The recorded symptoms that were considered significant included: 'difficulty breathing', 'cough', 'wheeze', 'chesty', 'bad chest', 'cyanosed', or 'poor feeding'. The length of hospital stay could not be determined for most of these patients, as PAS records did not exist before March 1994. A total of 360 children were identified and only 54 (admitted after March 1994) could be excluded because their hospital stay was less than 4 days. The medical notes were sought for the remaining 306 children with a view to searching through them all for evidence of CNEP use; however, only 191 notes could be traced. A search of these 191 notes identified 5 children as having received CNEP, but all 5 children were also identified from other sources.

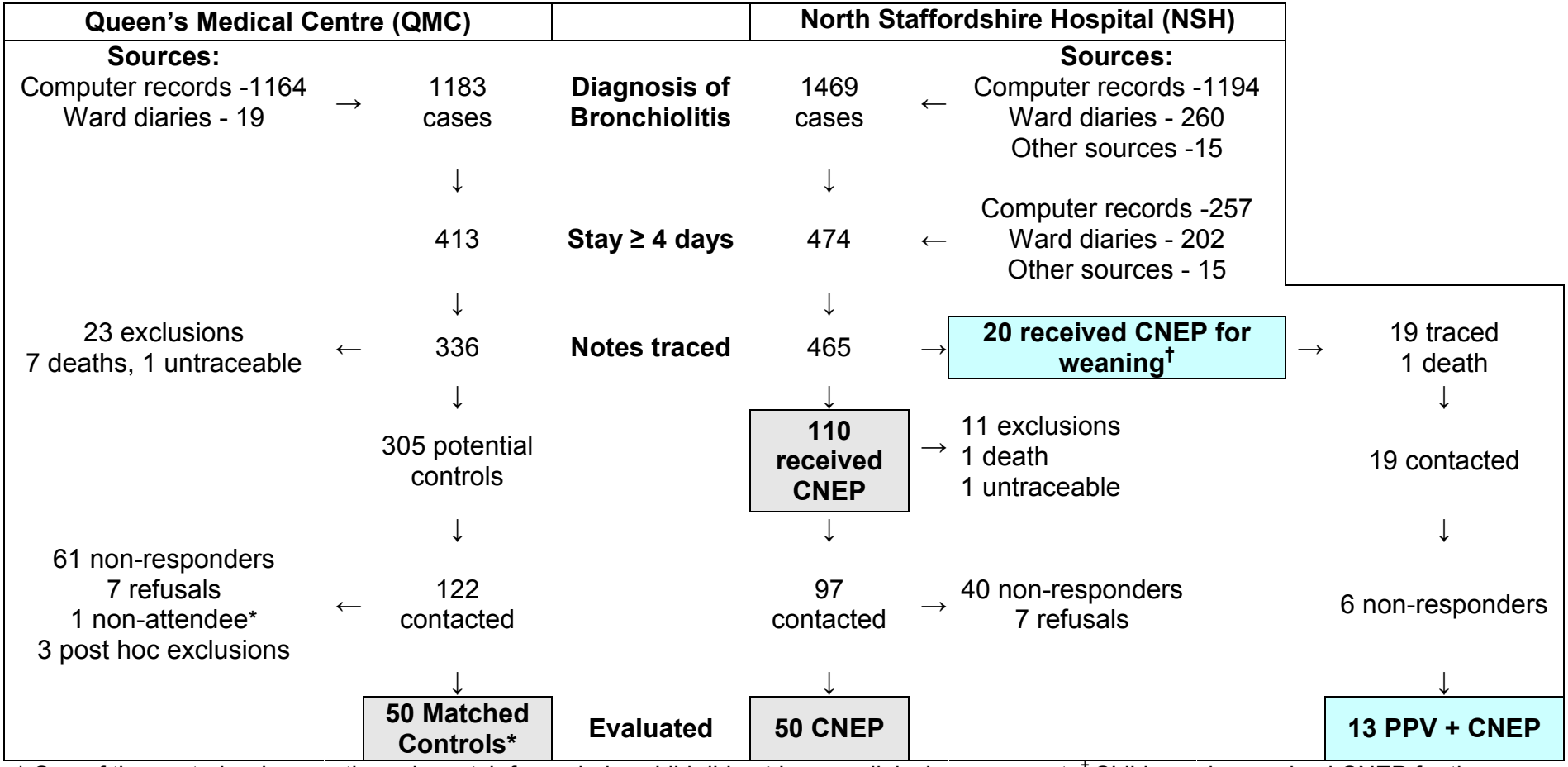
4.1.3 Physiology study

Eighteen children had participated in a study of 'The physiological effects of CNEP ventilation in infants with bronchiolitis' and were identified from the relevant study records. The study records included 9 children who received CNEP for bronchiolitis as well as 9 controls who did not receive CNEP. The notes were sought to ascertain which children were in the CNEP arm but four sets could not be traced. From the 14 sets of notes obtained, 8 children who had received CNEP were identified, 5 of whom had already been identified through the PICU and HDU ward diaries.

4.1.4 Self referral

Two children who had received CNEP were identified because their parents became aware of this study and contacted us to enquire about their eligibility to take part. Their notes were traced and the use of CNEP for bronchiolitis was confirmed.

Figure 7: Identification of the study population



* One of the controls who was the only match for an index child did not have a clinical assessment. † Children who received CNEP for the purpose of weaning from mechanical ventilation were evaluated separately without controls.

4.1.5 Exclusion criteria

Children were excluded from the study if they had any of the following:

1. Congenital cyanotic heart disease or non cyanotic heart disease requiring medication or associated with pulmonary hypertension.
2. Cystic fibrosis or other congenital anomaly involving the airway
3. Neuromuscular disease
4. Primary or secondary immune deficiency

4.1.6 Summary of study population - Index cases

- A total of 649 notes were searched and 130 children identified who had received treatment with CNEP.
- 7 children were excluded using the criteria above and another 4 because their notes revealed the diagnosis was not bronchiolitis.
- 99 children had received CNEP as primary treatment and 20 as an aid to weaning from conventional ventilation.
- 2 children had died after recovering from the bronchiolitis illness.
- A total of 50 children who had received CNEP as their primary treatment made up the final study population of index cases.
- 13 children who received CNEP to aid weaning from conventional ventilation are described as a separate group without controls.

4.2 Study Population – Comparison group

Computer records were available for children admitted to the Queen's Medical Centre (QMC) with a diagnosis of bronchiolitis between January 1993 and March 1999. As with the index cases the selection of notes to review was limited to those whose hospital stay was longer than 4 days. A further 19 children were found by searching a separate database of admissions to the PICU and by examining the PICU admission diaries; the notes were requested on all of these children. A total of 413 patients with a diagnosis of bronchiolitis and length of stay > 4 days were identified for the specified period. The notes of 336 children were traced and details recorded of their admission for bronchiolitis and of their neonatal history. Thirty one were excluded (exclusion criteria as in 4.1.5, above), had died or were untraceable, leaving 305 children as potential controls.

A matched control was selected for each index case with parental consent to participate in the study. When consent was withheld for a control child or no response was obtained after 2 letters, the next matching child was selected from the group of potential controls. Parents were given up to 6 weeks to respond to the first invitation letter before a second was sent. To improve recruitment and avoid delay in the final stages of the study, invitations were sent simultaneously to two controls for each index case. For one index case this resulted in two consented controls so the most closely matching was selected. Two

controls were replaced because subsequent to their recruitment, 2 others were identified who matched more closely. There were thus 3 controls at the end of the study who were unpaired and not included in the final analysis.

One of the controls failed to attend a follow up assessment despite written consent from a parent agreeing to participation in the study. As the only suitable match for a consented index case, this child was included in the study and their neonatal and bronchiolitis admission data (short term outcome data) were used in paired analysis.

4.3 Patient tracing and invitation letters

A study administrator used hospital records, the central NHS register and general practitioners as sources to trace the identified population. General practitioners were contacted to ensure that no child had died. A letter, originating from the lead consultant at each hospital, was sent to the parents of the identified children inviting them to participate in the study. Included with the invitation letters were information sheets (Appendices A, B and C) which explained the purpose and nature of the study in detail. Written informed consent was obtained from parents agreeing to participate in the study. The invitation letters, parent information leaflets and consent forms were designed by myself and revised by my supervisor. Ethical approval was obtained from the Local Research Ethics Committees in Stoke on Trent and Nottingham.

4.4 Matching

Cases were matched using the following criteria:

- Sex (male/female)
- Gestational age (<32 weeks, 32-36 weeks, >36 weeks)
- Illness severity (mild, moderate, severe) - Table 12
- Fraction of inspired oxygen (FiO_2) prior to ventilation

The FiO_2 just prior to starting CNEP was determined for all the index cases. Controls matching the first 3 criteria were then selected from the group of potential controls and matched for oxygen dependency. For those needing ventilation, FiO_2 just before ventilation was used for matching; for those admitted to PICU but not ventilated, FiO_2 just before admission to PICU was used; for controls treated on the general paediatric ward, the maximum FiO_2 given was used for matching.

4.5 Assessments

Children in the index group taking part in the study were assessed in a clinic setting adjacent to the North Staffordshire Hospital (NSH). Children in the control group were assessed in the Paediatric Respiratory Laboratory at the Queen's Medical Centre (QMC). Nine children (4 index cases, 5 controls) who had moved out of area, or whose parents were unable to attend either of these 2 centres, were visited at home. The parents of 2 children, who were recruited to a concurrent study of long-term outcome following the use of CNEP for

respiratory distress syndrome (RDS-CNEP study), gave consent to their participation in this study as well as they met the inclusion criteria for both. To avoid duplicating assessments, data acquired from these 2 children for the RDS-CNEP study were used in this study as well. Assessments for the RDS-CNEP study were carried out by a colleague (KT) and included an identical data-set to that needed for this study. I carried out all the other assessments with the assistance of a respiratory nurse (AS) for subjects seen at the QMC. The study nurse measured children's height, weight and blood pressure and assisted with the lung function testing.

4.5.1 Examination

Height was measured with the child wearing socks but no shoes. A calibrated wall fixed stadiometer (Holtain Ltd., Dyfed, UK) was used at the QMC whilst a portable, temporarily fixed stadiometer (Raven Equipment Ltd, Essex, UK) was used for home visits and at the NSH. Weight was measured in light clothing using *'Salter'* weighing scales (Jessops Ltd, Nottingham, UK). Head circumference was measured with a 'lasso' tape measure (Child Growth Foundation) or a standard tape measure. Height, weight and head circumference standard deviation scores (z-scores) were calculated using data provided by the Child Growth Foundation in a 'Microsoft Excel worksheet'. Blood pressure was measured with a mercury sphygmomanometer using an appropriately sized cuff. A respiratory examination was carried out to

identify any signs of acute or chronic respiratory disease and to measure the respiratory rate at rest. Neurological clinical examination was performed and documented in accordance with techniques described by Amiel-Tison and Stewart (1989). Examination findings were recorded in an assessment form (Appendix D). Criteria used to assess disability are detailed in Table 11.

4.5.2 Lung function tests

4.5.2.1 Airway resistance pre and post bronchodilator

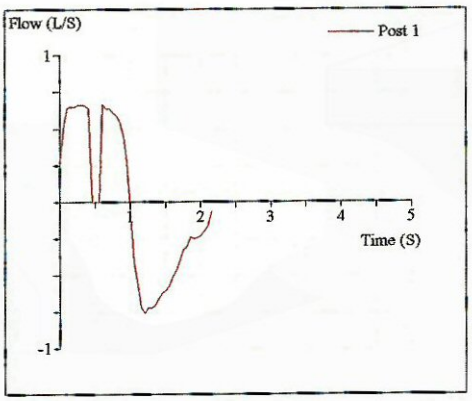
Airway resistance (*R*int) was measured using a 'Microlab 4000' Micro-Rint^{TM} device (Micro Medical Ltd, Gillingham, UK). Two identical Micro-Rint^{TM} devices were shared between this study and another which was running concurrently (RDS-CNEP study). To minimise the chance of any small differences between devices, the same Micro-Rint^{TM} device was used whenever possible. It was necessary to use the second device to test 4 children in the control group because the first device was in use at the time. Subjects were seated in a comfortable position and were distracted with a puzzle book during the procedure. They were encouraged to breathe quietly through a plastic mouthpiece with a nose-clip in place and their cheeks supported from behind. If a nose clip was not tolerated, the child's nose was occluded by the investigator's fingers whilst also supporting their cheeks. Ten consecutive measurements were taken at random intervals during expiration and the median value of at least 6 acceptable measurements

was taken. Values were considered acceptable when both the 'flow-time curves' and 'pressure-time curves' were of consistent shape (Phagoo et al., 1996); examples of acceptable and non-acceptable curves are shown in Figure 8. Airway resistance was repeated after the administration of 500 micrograms of salbutamol administered through a spacer device (Volumatic; Allen & Hanburys, UK) in all children who were able to perform adequate baseline lung function testing.

4.5.2.2 Spirometry including reversibility studies

Spirometry was performed using a Fleisch Pneumotachograph Spirometer 2120 (Vitalograph Ltd., Buckingham, UK) on all index cases and all but 4 of the controls. A second Fleisch Pneumotachograph Spirometer (Vitalograph Ltd., Buckingham, UK) was used on 4 children in the control group due to the first device being in use. Both devices were connected to a personal computer with spirotrac 4.20 software, which includes an incentive display. The spirometer was calibrated at the beginning of each test day with a 1-litre syringe (Vitalograph Ltd.) after adjusting for room temperature. Children were coached, by me or the study nurse, to perform the test in a standing position; the best of 3 acceptable attempts was chosen in accordance with standardised criteria (Miller et al., 2005). The FEV_1, FVC and FEF_{25-75} were recorded and spirometric measurements were repeated after inhalation of salbutamol 500 micrograms through a spacer device (Volumatic; Allen & Hanburys, UK) in all children who were able to perform adequate baseline lung function testing.

Figure 8: Examples of Rint Flow/Time and Pressure/Time curves obtained



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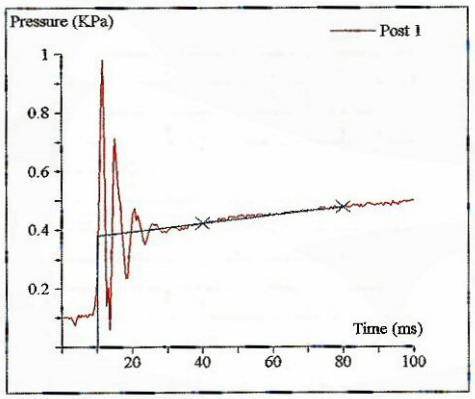

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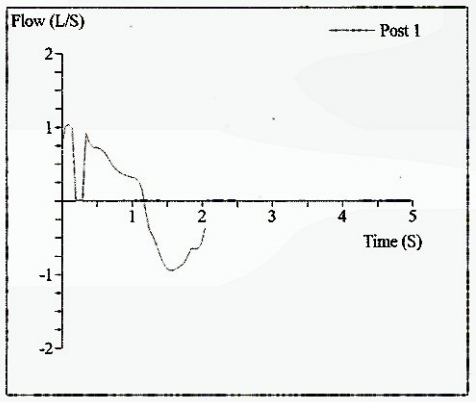

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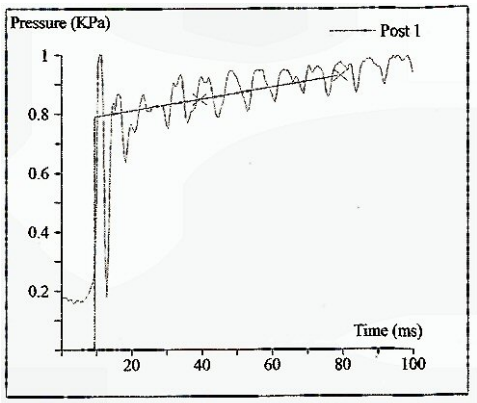

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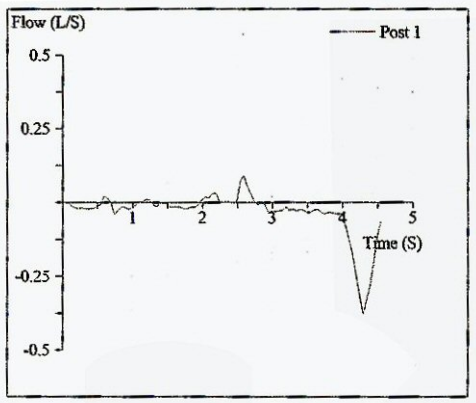

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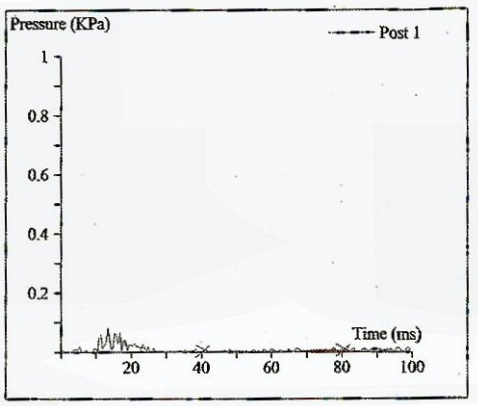

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4.5.3 Data collected from medical notes

Details of the admission for bronchiolitis and neonatal history were mostly obtained from the medical notes. In a few cases, however, data were incomplete because of prior or subsequent treatment in a district general hospital (DGH); in these cases a letter was sent to the General Practitioner or DGH consultant to request the missing data.

4.5.4 Data collected using questionnaires

Parents completed questionnaires (Appendices E and F) detailing disability, demographics, current health, family history, prior respiratory or neurological morbidity; they also completed the Strengths and Difficulties Questionnaire to quantify behaviour problems (Goodman, 1999) and the Health Utilities Index (HUI-3) to assess health related quality of life (Feeny et al., 1996). An assessment of disability was made partly by clinical examination (Appendix D) and partly from information recorded in the parent and medical history questionnaires. The medical history questionnaire (Appendix E) was completed by interview of the parents whilst the parent questionnaire (Appendix F) was completed independently.

4.6 Statistical analysis

Data were entered into SPSS v11.5 and encoded for further analyses. In view of the matched-pairs design, statistical methods appropriate for

paired data were used throughout the analyses unless the number of pairs where insufficient to justify its use. The sign test was used to compare matched pairs of continuous data (Armitage, 2002). Although this test has low statistical power, no assumptions are made on the shape of the probability distribution the observations are from. For paired categorical data with binary outcomes the Mantel-Haenszel statistic with 95% confidence intervals has been used (Rothman and Greenland, 1998) and for more than two categories the marginal symmetry of the outcomes was tested using the Stuart-Maxwell test. For outcomes in which there were insufficient pairs, a Mann Witney U test was used for continuous data and relative risk or a chi-squared for categorical data.

4.7 Ethical issues

Ethical approval was obtained from the Local Regional Ethics Committees in Stoke on Trent and Nottingham prior to starting the study (Appendix G). Written informed consent was obtained from the parents or guardians of all children participating in the study.

4.8 Funding

The study was funded by the West Midlands Regional Health Authority, through the University Hospital of North Staffordshire NHS Trust, by a grant to the University of Nottingham.

5 Results

A comprehensive search of NSH records for patients admitted with bronchiolitis and treated with CNEP identified 130 children who received this mode of respiratory support. Twenty children received CNEP as an aid to weaning from PPV whilst 110 received CNEP as primary treatment. One hundred and sixteen children who were traced and found to be eligible for the study (97 treated primarily with CNEP, 19 who had CNEP for weaning from PPV) were invited to participate. Parental consent was obtained for 63 children (54%). Fifty of the 97 children (51%) who received CNEP as their primary treatment were evaluated with an equal number of matched controls; 13 of the 19 children (68%) who received CNEP to aid weaning from PPV were evaluated without controls. Data for the children who received 'CNEP for weaning' are shown alongside those of children in the matched cohort study in Table 13 and in Figures 9-35. Other data for the children in the 'CNEP for weaning' group are listed in section 5.2.

5.1 Matched cohort study

5.1.1 Non-responders or refusals

Audit data collected on all children who received CNEP as primary treatment during the period of interest shows that the median FiO_2 prior to ventilation in those not recruited was 0.37, median gestation at birth was 36 weeks and 83% were RSV positive. These factors do not differ significantly from those of children who were recruited to the study

(p=0.23, p=0.76, p=0.23 respectively; Mann-Whitney U test). Children recruited to the study were more likely than the non-responders or refusals to be male (32 v 20; p=0.035) and to have a severe illness (78% v 49%); they were less likely to have a moderate illness (22% v 51%; χ^2 p=0.003).

5.1.2 Matching details

Table 13: Population characteristics

	CNEP (n=50)	Controls (n=50)	CNEP for weaning (n=13)	Non-responders or refusals (n=47)*
Matching Criteria				
Male	32 (64%)	32 (64%)	5 (39%)	20 (43%)
Median gestational age at birth (weeks)	37	37.5	36	36
Gestation age bands				
< 32 weeks	9	9	2	11
32-36 weeks	15	15	5	13
≥ 37 weeks	26	26	6	22
Illness severity				
Mild	0	0	0	0
Moderate	11	11	0	24
Severe	39	39	13	23
Median $Fi0_2$	0.28	0.40	0.41	0.37
	(n=50)	(n=49)	(n=13)	(n=47)
Median age at study evaluation (years)	6.4	7.7	6.7	-
(Range)	(4.5 -11.0)	(5.2 -11.5)	(5.2 - 10.8)	
RSV positive	45 (90%)	44 (90%)	11 (85%)	39 (83%)
Ethnic Group				
White	47	44	10	-
Mixed	1	3	3	-
Asian	2	1	0	-
Black	0	1	0	-

* The gestational age at birth was not recorded in the medical notes for a child who was a refusal.

Details of the matching criteria and characteristics of the non responders or refusals are listed in Table 13 above. Fourteen children in the CNEP cohort (28%) received both intermittent (INEP) and continuous negative extrathoracic pressure (CNEP); 36 (72%) received CNEP alone. Thirty three children treated with CNEP and 27 controls had evidence of respiratory failure defined using criteria reported by Outwater and Crone (1984); this was not significantly different between the groups (p=0.35). The criteria included: hypercarbia ($paCO_2 \geq 8.0$ kPa) with or without respiratory acidosis, persistent hypoxia ($paO_2 \leq 8.0$ kPa despite $FiO_2 \geq$ 40%), metabolic acidosis, apnoea or bradycardia. The median pCO_2 in the CNEP group was 8.5 kPa, (IQR 7.0 - 9.8) [n=28] prior to starting respiratory support and in the controls was 8.8 kPa, (IQR 8.03 -11.7) [n=19]; p=1.00. The pCO_2 measurement used in analysis was that recorded just prior to respiratory support if the child was ventilated, otherwise it was the measurement prior to admission to PICU or at the point of maximum oxygen dependency. A child in the control group with a pCO_2 measurement of 25.2kPa (outlier) had a corresponding pH of 6.9 and from the records appears to have required immediate intubation and ventilation. The result has therefore been included in the analysis as a true measurement. Figure 9 is a scatter plot of pCO_2 measurements.

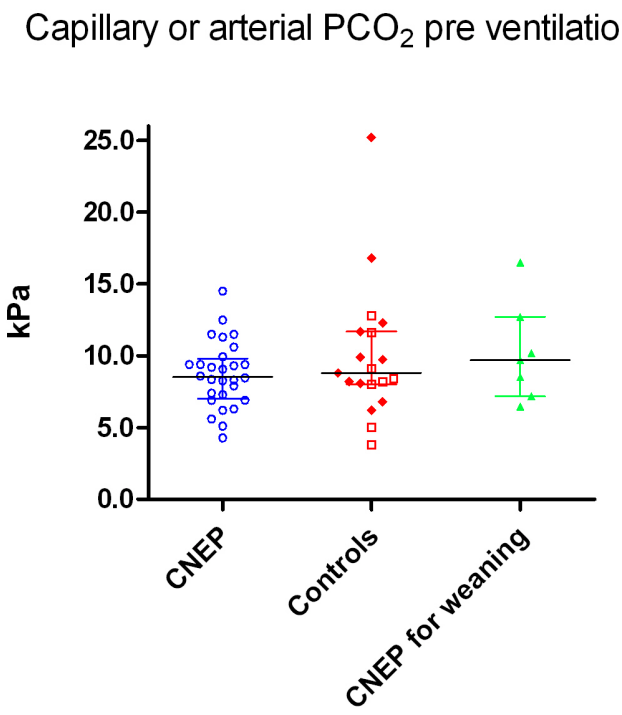

Figure 9: Scatter plot of 'pre-ventilation' capillary or arterial pCo_2 with median values and interquartile ranges showing no significant difference between the CNEP cohort and their controls. The diamond shaped data points represent controls who received positive pressure respiratory support. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

Children in the control group were on average 1.25 years older than children in the CNEP cohort at the time of assessment. Age was partly controlled for by matching from a cohort of children treated at a similar time as those receiving CNEP. The groups were well matched in respect to the stipulated criteria other than for the pre-ventilation FiO_2. Thirty-six cases were matched with controls within a FiO_2 range of +/- 10% and 45 cases were matched within a range of +/- 15% (1 SD). Each of the 5 CNEP cases that could not be matched within this range had FiO_2

between 0.24 - 0.28 before commencing ventilation. They were matched with controls whose F_IO_2 ranged from 0.40 - 0.47 (F_IO_2 differences: +0.16, +0.16, +0.18, +0.19 and + 0.21, respectively). Just over half of infants treated with CNEP were receiving nasal cannula oxygen prior to starting respiratory support compared to just 14% of the controls. Almost 75% of controls were receiving headbox oxygen (Table 14).

Table 14. Different modes of oxygen delivery in the CNEP and control cohorts

	Nasal prongs	Head box	Face mask
CNEP	27	18	5
Controls	7	37	6

5.1.3 Demographic and neonatal variables

Demographic details of the 2 groups are shown in Table 15. There were no significant differences in birth weight, parental age, social class or other demographic information. There was a trend towards increased prenatal smoking amongst mothers in the CNEP group; parents who were current smokers were not significantly different between the groups. One child in the CNEP cohort was a smoker; none of the children in the control group reported being a smoker.

A range of demographic details and neonatal variables were evaluated in the 2 groups and are shown in Tables 15 and 16. Equal numbers of children in the CNEP and control cohorts were admitted to the neonatal intensive care unit. The rates of intubation at birth and subsequent ventilation on NICU were not significantly different between the groups. Four children in the CNEP group compared to none of the controls had had intraventricular haemorrhages in the neonatal period; this was not significantly different between the groups.

Table 15: Demographic information of children in the CNEP and control cohorts; comparisons made with Sign tests or Mantel-Haenszel statistic as appropriate

	CNEP	Range	Controls	Range	Number of pairs	'p'
Median birth weight (grams)	2597 [n=50]	975 - 4479	2800 [n=49]	820 - 4479	49	0.15
Median maternal age (years)	34 [n=48]	22 - 48	36 [n=48]	25 - 51	46	0.46
Median paternal age (years)	39 [n=44]	23 - 53	39 [n=44]	29 - 64	39	0.14
Median [a]overcrowding index	1.20 [n=50]	0.5 - 2.7	1.25 [n=45]	0.7 - 2.3	45	0.11
	CNEP	Controls	Number of pairs	Mantel-Haenszel statistic	95% confidence intervals	'p'
Maternal social class Manual Non-manual	[n=49] 32 17	[n=48] 24 24	47	1.25	0.93 to 1.67	0.13
Paternal social class Manual Non-manual	[n=44] 28 16	[n=42] 23 19	39	1.25	0.89 to 1.76	0.20
Current smokers in household	28 [n=50]	19 [n=49]	49	1.42	0.86 to 2.35	0.17
Maternal smoking in pregnancy	23 [n=50]	14 [n=50]	50	1.64	0.95 to 2.84	0.07
Receiving benefits	36 [n=50]	34 [n=48]	48	1.03	0.87 to 1.22	0.74
Maternal use of a car	35 [n=49]	37 [n=48]	47	0.92	0.71 to 1.19	0.51
Paternal use of a car	26 [n=45]	29 [n=45]	40	0.89	0.66 to 1.21	0.47

[a]Overcrowding index = (Number of adults + children in the household)/ Number of rooms

Table 16: Neonatal information of children in CNEP and control cohorts; comparisons made using Mantel-Haenszel statistic or Mann Whitney U test

	CNEP [n=50]	Controls [n=50]	Mantel-Haenszel statistic	95% C.I.	'p'
NICU admission	22	22	1.00	0.75 to 1.33	1.00
Intubated at birth	8	6	1.33	0.60 to 2.97	0.48
Ventilated in NICU	7 [n=22]	12 [n=22]	0.58	0.29 to 1.19	0.13
Intraventricular haemorrhage	4 [n=6]*	0 [n=6]*	-	-	0.16
Postnatal steroids for chronic lung disease	2	1	0.00	-	0.32
Neurological abnormality suspected at birth	4	2	2.00	0.50 to 8.00	0.32
	CNEP	Range	Controls	Range	'p'
Median number of days ventilated (NICU)	4 [n=7]	1 - 38	3.5 [n=12]	1 - 33	0.27
Median number of days in oxygen (NICU)	4 [n=15]	1 - 301	5 [n=10]	1 - 75	0.33

* There were 3 children in both cohorts who were preterm (<32weeks) but had no recorded cranial ultrasound findings

5.1.4 Outcome evaluations

5.1.4.1 Primary outcome measure

Nine children (6 CNEP, 3 controls) were unable to cooperate sufficiently with testing for *R*int due to their young age or developmental problems. Median baseline *R*int (% predicted) was significantly higher in the CNEP group compared to controls: CNEP 99.5%, Controls 83%; p<0.001 (Figure 10, Table 17) but there was no significant difference in the percentage (%) change *R*int after bronchodilator treatment (Figure 11, Table 17). This showed a median 31.8% fall in the CNEP group and a 29.6% fall in controls; p=0.43 (Table 17). The median bronchodilator response ratio (BDR ratio) was1.47 (Range 0.89 - 2.48) for children treated with CNEP and 1.42 (Range 0.92 - 2.56) for controls; p=0.43, [n= 40 pairs]. Thirty three children treated with CNEP [n=44] and 31 controls [n=46] had a BDR ratio ≥ 1.22; in paired analysis the relative risk of CNEP being associated with a BDR ratio ≥ 1.22 was 1.07, 95% C.I. 0.80 -1.43, n=40 pairs; p=0.64. The effect of tobacco smoke exposure on the observed difference in *R*int has been further explored by stratifying the data to evaluate pairs in the CNEP and control cohorts where the exposure was similar. For the 6 pairs of children who had smoking parents in the home the median *R*int value was 93% - CNEP group (range 80-113%) and 83% - Control group (range 66 - 103%; p=0.031). For 8 pairs of children whose parents were non smokers the median *R*int value was 93.5% - CNEP group (range 75 - 159%) and 75% - Control group (range 44% - 112%; p=0.07).

5.1.4.2 Other respiratory outcome measures

Thirteen children (9 CNEP, 4 controls) were unable to perform spirometry. All lung function tests were adequately performed by 39 children in the CNEP cohort [n=50] and 45 children in the control group [n=49]; this was not significantly different between the two groups although there was a trend towards more success in controls (Mantel-Haenszel statistic 0.87, 95% CI: 0.74 -1.02; p= 0.08). FEV_1 and FVC were not significantly different in the two groups and showed similar change after bronchodilator treatment (Figures 12-15). In contrast median FEF_{25-75} was significantly lower in the CNEP group - 77.5% predicted compared to controls - 86.8% predicted; p=0.029 (Figure 16). The percentage change FEF_{25-75} was not significantly different between the groups (Figure 17). The significant difference found in baseline FEF_{25-75} supports the finding of higher airway resistance in the CNEP cohort.

The frequency of wheeze and inhaled medication use was similar in the two groups (Table 19, Figures 21 and 22) and there were no differences in the number of intrinsic or extrinsic risk factors for asthma. No child was admitted to hospital with a respiratory illness in the 12 months before being assessed.

5.1.4.3 Short term outcome measures

Short term outcome measures are shown in Table 18. Children in the CNEP cohort spent an average of 2 days longer in supplemental oxygen; p=0.037 (Table 18, Figure 19) and stayed in hospital an extra 1.8 days compared to controls; p=0.087 (Table 18, Figure 18). In contrast they received PPV less frequently (6 versus 18; p=0.005) and if ventilated, spent a shorter period receiving IPPV; p=0.004 (Table 18, Figure 20) compared to their matched controls. Twenty six children treated with CNEP and 23 controls were admitted to PICU (p=0.49).

Table 17: Results of lung function testing of children in the CNEP and control cohorts; comparisons made with Sign test.

		CNEP	Range	Controls	Range	Number of pairs	'p'
Baseline Airway Resistance	($kPaL^{-1}s^{-1}$)	0.71 [44]	0.31 to 1.19	0.56 [47]	0.27 to 1.53	41	**0.003**
	(% predicted)	99.5 [44]	54.0 to 160.0	83.0 [47]	44.0 to 225.0	41	**<0.001**
Airway Resistance post bronchodilator	($kPaL^{-1}s^{-1}$)	0.48 [44]	0.21 to 1.00	0.41 [46]	0.18 to 0.92	40	**0.025**
	(% predicted)	68.0 [44]	40.0 to 118.0	59.5 [46]	29.0 to 139.0	40	**0.025**
% change in Airway Resistance		-31.8 [44]	-60.0 to 13.0	-29.6 [46]	-61.0 to 9.0	40	0.43
FEV_1	(% predicted)	86.3 [41]	48.3 to 112.1	88.5 [46]	56.9 to 119.3	39	0.52
FEV_1 post bronchodilator	(% predicted)	98.0 [39]	60.6 to 114.9	97.2 [43]	73.5 to 124.5	36	0.62
% change in FEV_1		11.7 [39]	-7.2 to 58.6	10.7 [43]	-6.8 to 32.2	36	0.13
FVC	(% predicted)	96.9 [41]	69.8 to 121.5	93.9 [48]	61.4 to 123.2	40	0.08
FVC post bronchodilator	(% predicted)	102.7 [40]	84.1 to 121.7	100.1 [47]	55.9 to 122.3	38	0.63
% change in FVC		6.0 [40]	-11.6 to 38.5	5.9 [47]	-9.9 to 24.3	39	0.63
FEF_{25-75}	(% predicted)	77.5 [42]	13.7 to 196.6	86.8 [48]	33.9 to 127.5	40	**0.029**
FEF_{25-75} post bronchodilator	(% predicted)	93.9 [41]	26.6 to 192.7	102.4 [47]	57.5 to 173.7	39	0.34
% change in FEF_{25-75}		23.3 [41]	-13.3 to 173.8	27.2 [47]	-10.6 to 83.2	39	1.00

[n]= number of children who successfully completed the test, FEV_1 = Forced expiratory volume in 1 second, FVC = Forced vital capacity, FEF_{25-75} = Forced expiratory flow between 25% and 75% of forced vital capacity.

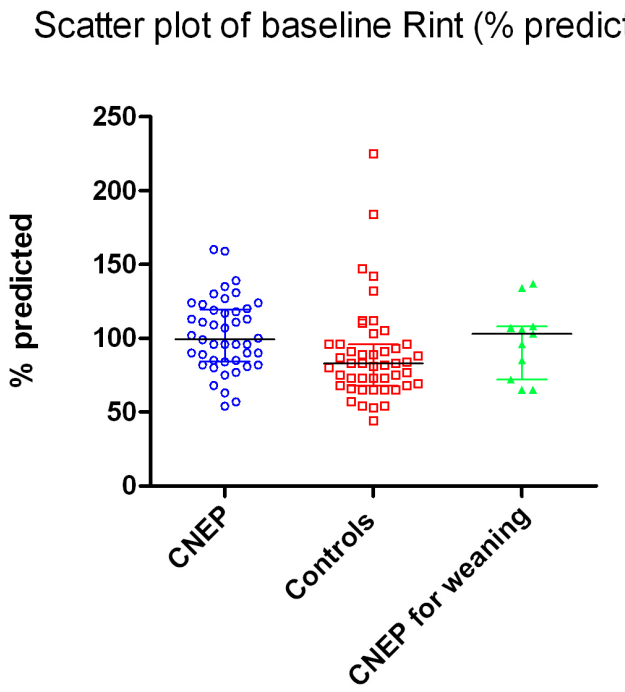

Figure 10: Scatter plot of baseline Rint with median values and interquartile ranges showing a significant difference in baseline Rint between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

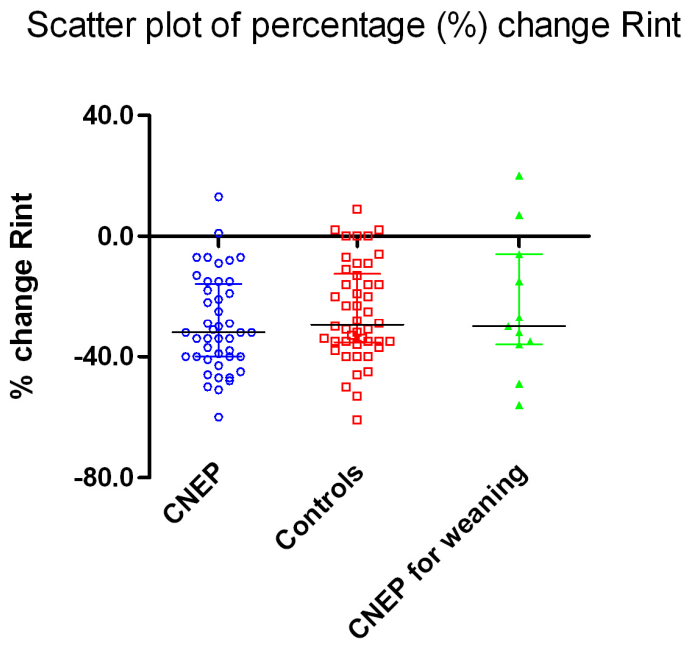

Figure 11: Scatter plot of % change Rint with median values and interquartile ranges showing no significant difference in the % change Rint following a bronchodilator. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

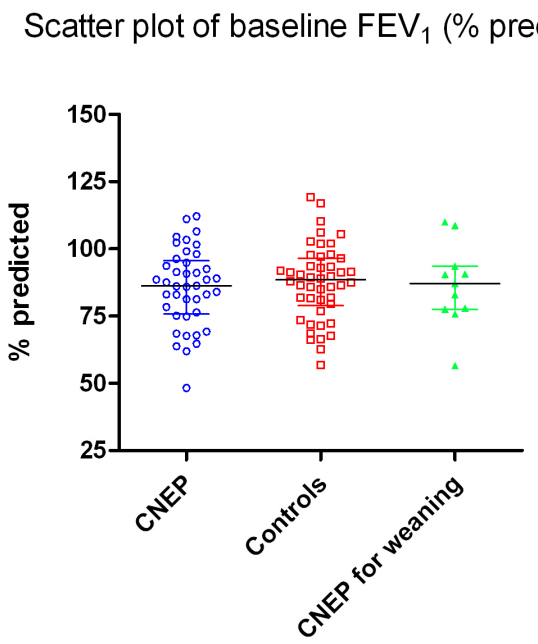

Figure 12: Scatter plot of baseline forced expiratory volume in 1 second with median values and interquartile ranges showing no significant difference between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

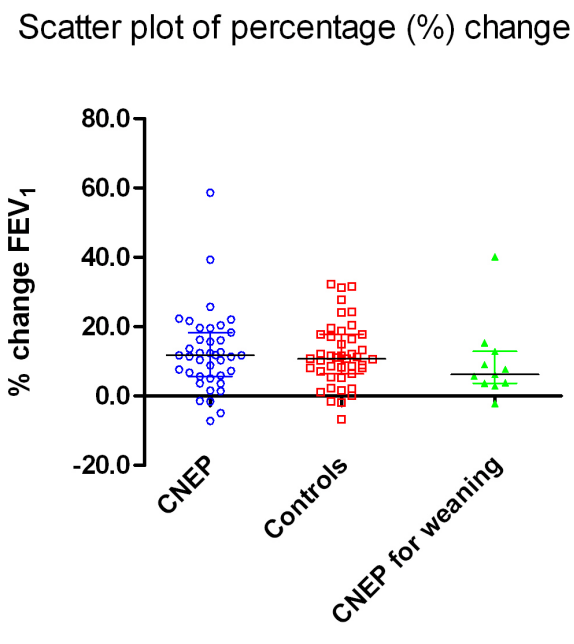

Figure 13: Scatter plot of % change forced expiratory volume in 1 second with median values and interquartile ranges showing no significant difference between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

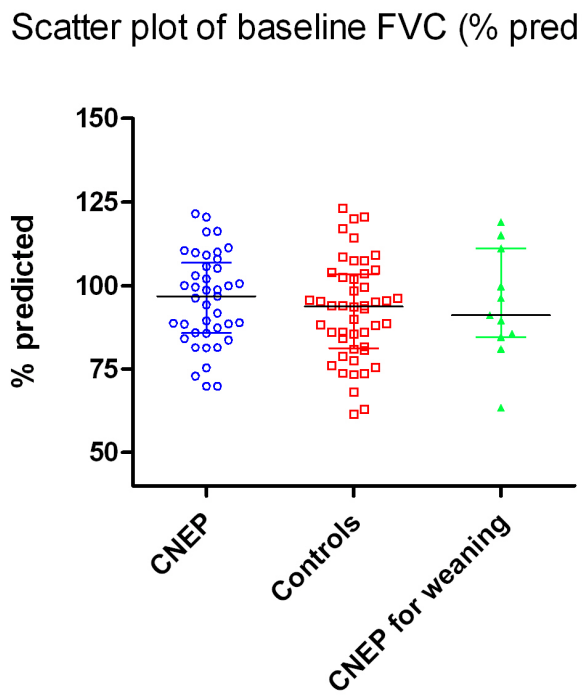

Figure 14: Scatter plot of baseline forced vital capacity with median values and interquartile ranges showing no significant difference between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

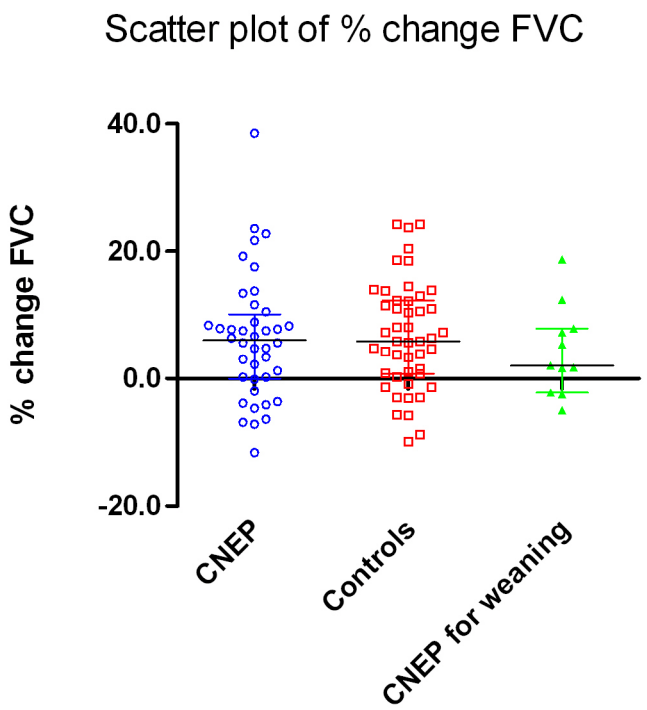

Figure 15: Scatter plot of % change forced vital capacity with median values and interquartile ranges showing no significant difference between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

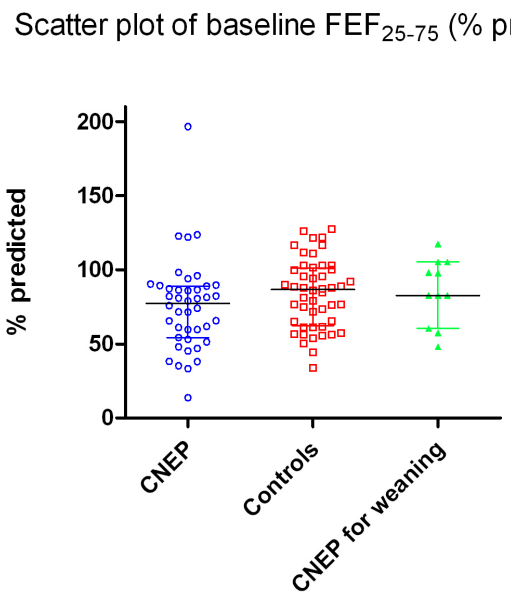

Figure 16: Scatter plot of baseline FEF_{25-75} with median values and interquartile ranges, showing a significant difference between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

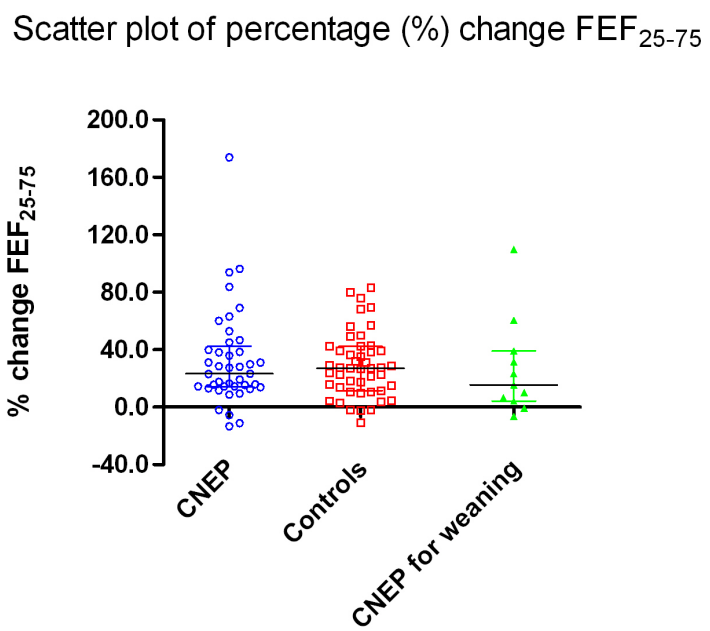

Figure 17: Scatter plot of %change FEF_{25-75} with median values and interquartile ranges, showing no significant difference between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

Table 18: Variables associated with the index bronchiolitic illness in the CNEP and control cohorts; comparisons made with the Sign test or Mann-Whitney U test as appropriate.

	CNEP [n=50]	Range	Controls [n=50]	Range	No of pairs	'p'
Median age at admission with bronchiolitis (weeks)	9.3	1 -71	8.0	2 -54	50	0.89
Median time to ventilation, to PICU admission or to maximum FiO_2 (hours)	24.5	1 -138	18.5	1 -127	39	0.87
Median length of stay in hospital with bronchiolitis (days)	9 [n=46]	5 -26	8 [n=50]	4 - 25	46	**0.017**
Median duration of oxygen therapy with bronchiolitis illness (days)	8 [n=45]	4 -23	5 [n=48]	1 -23	43	**0.035**
Median duration of nasogastric or intravenous feeding (days)	4.5	0 -20	4.5	0 -21	50	0.56
Median duration of CNEP (days)	3.5	1 -15	N/A	-	-	-
	CNEP	Range	Controls	Range		'p'*
Median length of stay on PICU (days)	2 [n=26]	1 - 10	4 [n=23]	1 - 18	-	0.80
Median duration of IPPV/ CPAP (days)	4.5 [n=6]	1 - 9	5.5 [n=18]	1 - 15	-	**0.004**

* Mann-Whitney U test

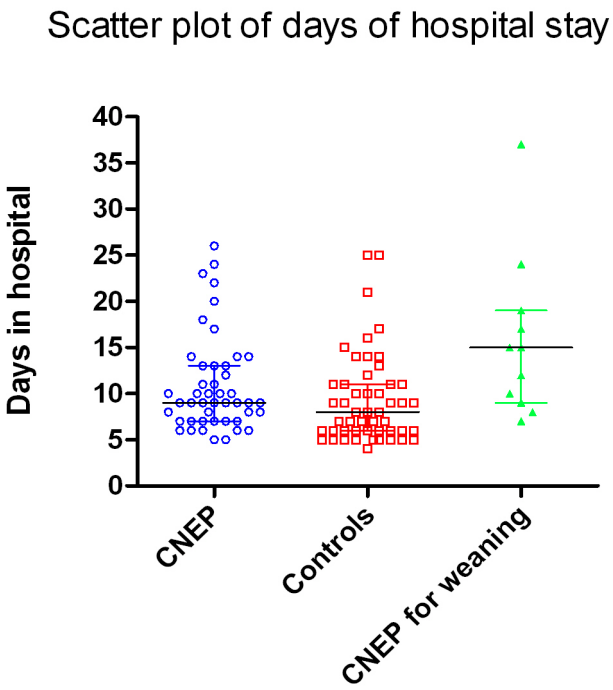

Figure 18: Scatter plot of days hospital stay with median values and interquartile ranges showing significantly longer hospital stay in the CNEP cohort compared to their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

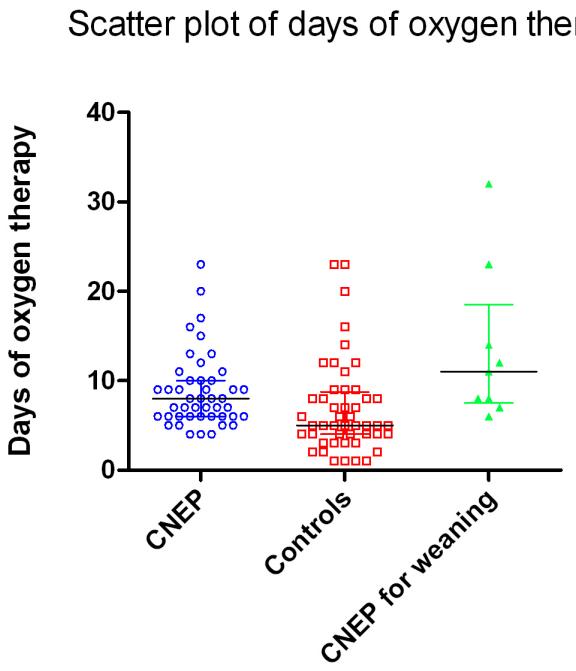

Figure 19: Scatter plot of days of supplementary oxygen therapy with median values and interquartile ranges showing significantly more days of oxygen therapy in the CNEP cohort compared to their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

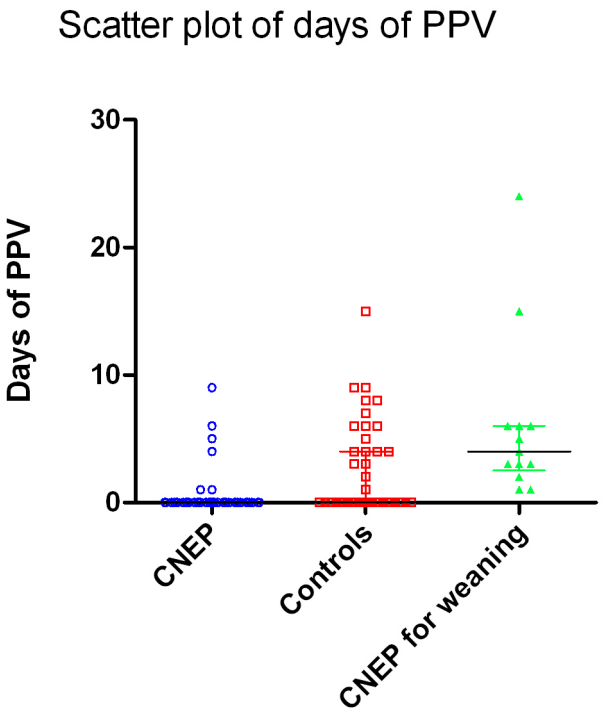

Figure 20: Scatter plot of days of positive pressure ventilation with median values and interquartile ranges showing significantly fewer days of PPV in the CNEP cohort compared with their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

Table 19: Respiratory outcomes reported by parents showing no significant difference between the CNEP and control cohorts; comparisons made using Mantel-Haenszel statistic

	CNEP [n=50]	Control [n=49]	Mantel-Haenszel statistic	95% C.I.	'p'
Any wheezing in previous 12 months	15	13	1.15	0.66 to 2.02	0.62
Ever diagnosed asthma	18	19	0.95	0.58 to 1.54	0.83
Follow up by a paediatrician for respiratory disorder	4	2	2.00	0.37 to10.92	0.41
Current use of bronchodilators	11	16	0.94	0.85 to 1.03	0.18
Current use of steroid inhalers	7	11	0.64	0.26 to 1.55	0.32
Frequency of wheeze in previous 12 months‡					
No wheeze	35	36			
Occasional wheeze (1-3 episodes)	7	10	-	-	0.30
Moderate wheeze (4 -12 episodes)	8	0			
Frequent wheeze (> 12 episodes)	0	3			
No. of extrinsic* factors					
None	24	22			
1	22	22	-	-	0.95
2	3	3			
3	1	2			
No. of intrinsic† factors					
None	12	4			
1	9	10	-	-	0.24
2	7	7			
≥3	22	28			

* Extrinsic factors = Damp, mould, long haired or feathered pets, †Intrinsic factors = Family history of asthma, hay fever or chronic chest problem, ‡ assessed with the Stuart Maxwell Statistic

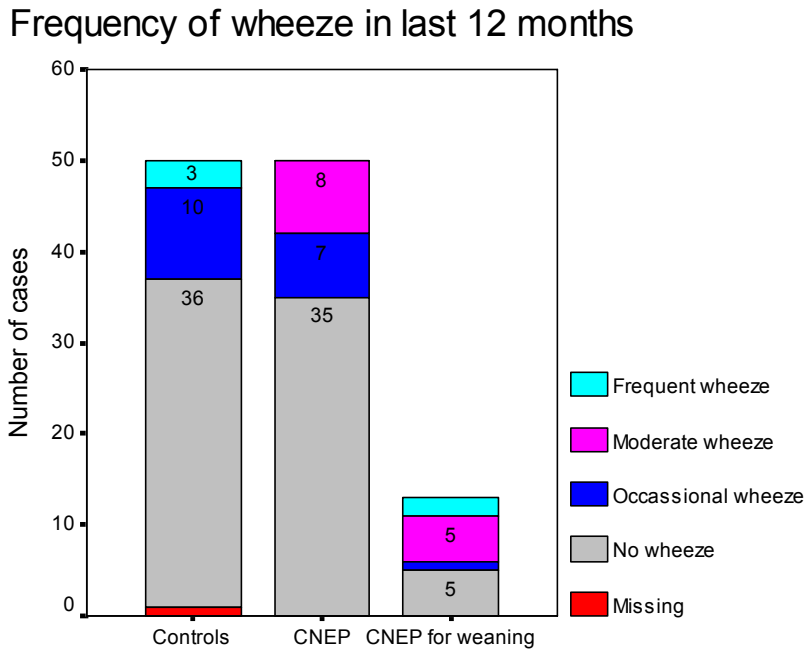

Figure 21: Stacked bar graph of the frequency of wheezing in the 12 months prior to assessment; no significant difference was found between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

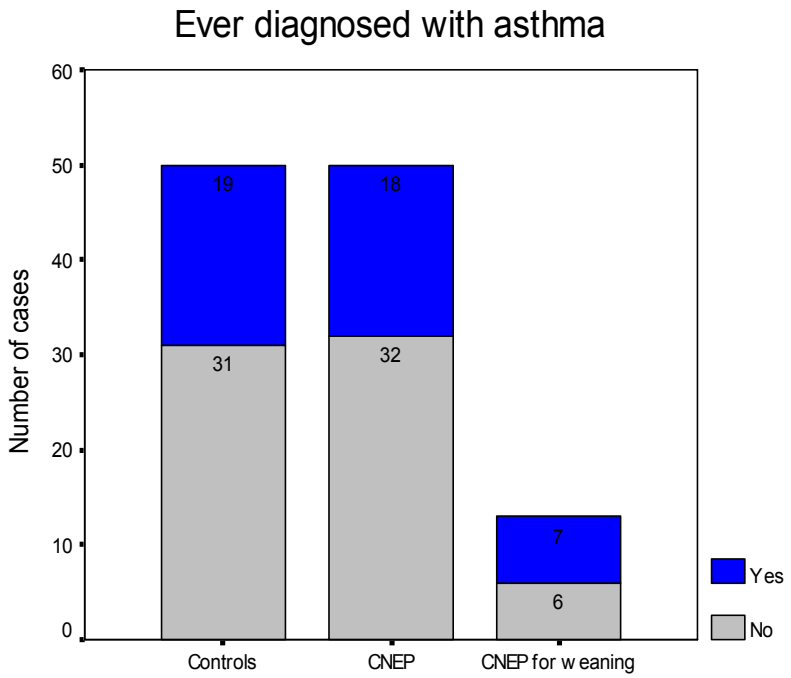

Figure 22: Stacked bar graph showing whether or not a diagnosis of asthma had been made at any time previously; no significant difference was found between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

5.1.4.4 Functional outcome measures

One child in the control group did not have a clinical or respiratory assessment and so their paired CNEP child, who was assessed to have a moderate or severe disability, was removed from this analysis, leaving 49 sets of paired data (Table 20). Of the remaining children, 14 in the CNEP group had moderate or severe disability compared to 10 in the control group (Figure 23); this was not significantly different between the groups, Mantel-Haenszel statistic 1.40 (95%CI: 0.64 to 3.04). An unexpectedly high proportion of children in both groups were identified as having a moderate or severe disability because of high behavioural scores. Without this domain, 7 children had moderate or severe disability in the CNEP group compared to 5 in the control group (Figure 24); this also was not significantly different between the groups, Mantel-Haenszel statistic 1.40 (95%CI: 0.49 to 3.99). No significant difference was found between the groups in any of the individual disability domains (Figures 25-30, Table 20). Figure 31 and Table 22 show the frequency and types of diagnoses known to be associated with disability which parents were aware of prior to their childrens' treatment for bronchiolitis. At assessment 1 child in the CNEP group and 2 children in the control group had cerebral palsy (CP). The CNEP child had ataxic type CP; one of the controls had unilateral spastic CP and the other had bilateral spastic CP. A possible association between the use of CNEP and upper limb coordination problems has previously been reported; no significant difference was found between the groups for this outcome measure (Table 21).

Table 20: Disability by pair within 6 domains showing no significant differences between the CNEP and control cohorts; comparisons made using Mantel-Haenszel statistic.

	CNEP *[n=49]	Controls * [n=49]	Mantel-Haenszel statistic	95% C.I.	'p' value
Moderate or severe cognitive disability	5	2	2.5	0.5 to 12.9	0.26
Moderate or severe neuromotor disability	4	4	1.0	0.3 to 3.3	1.00
Moderate or severe visual disability	1	1	1.0	0.1 to 16.0	1.00
Moderate or severe hearing disability	0	0	-	-	-
Moderate or severe behaviour disability	11	6	1.8	0.7 to 5.0	0.23
Moderate or severe other disability	6	3	2.0	0.6 to 6.8	0.26
Any moderate or severe disability	14	10	1.40	0.64 to 3.04	0.39
Any moderate or severe disability (excluding behaviour)	7	5	1.40	0.49 to 3.99	0.53

* One child in the control group did not have a clinical assessment and so their paired CNEP child, who was assessed to have a moderate or severe disability was removed from this analysis leaving 49 sets of paired data.

Table 21: Upper limb function in CNEP and control cohorts; comparisons made using Stuart-Maxwell test.

	Normal	Impairment	Mild clumsiness	Able to feed and dress but requires aids or assistance for some tasks	Severe difficulty with fine movements, requires aids or assistance	Total
Controls	45	0	3	1	0	49
	91.8%	0%	6.1%	2.0%	0%	100.0%
CNEP	43	0	3	3	1	50
	86.0%	0%	6.0%	6.0%	2.0%	100.0%

Stuart-Maxwell test for a 4x4 table performed; χ^2 test statistic 1.36, p=0.71

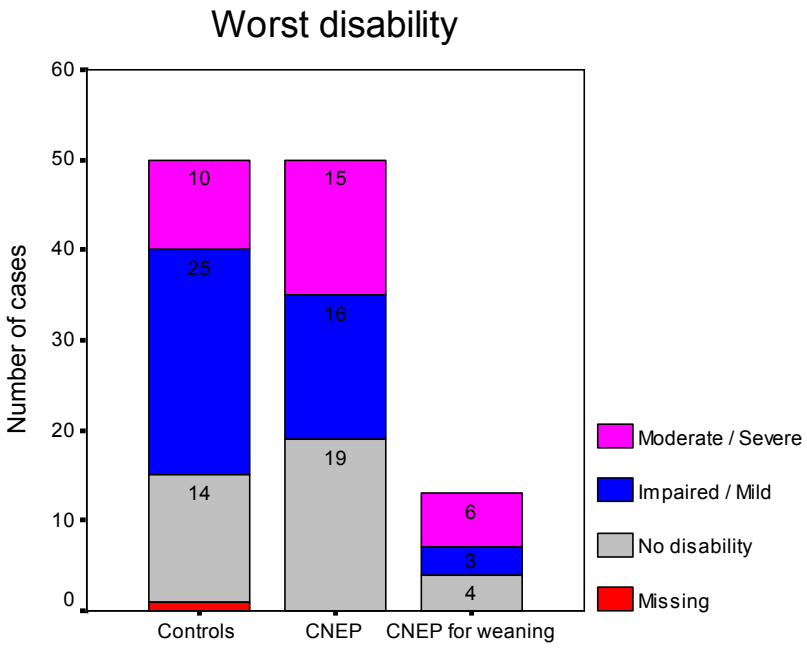

Figure 23: Stacked bar graph of worst disability scores; no significant difference was found between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

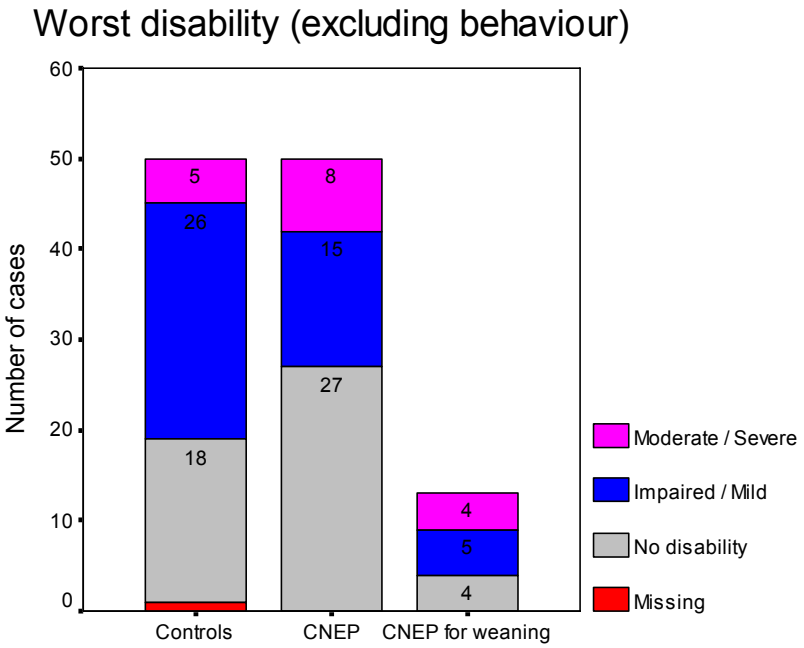

Figure 24: Stacked bar graph of worst disability scores without behavioural domain; no significant difference was found between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

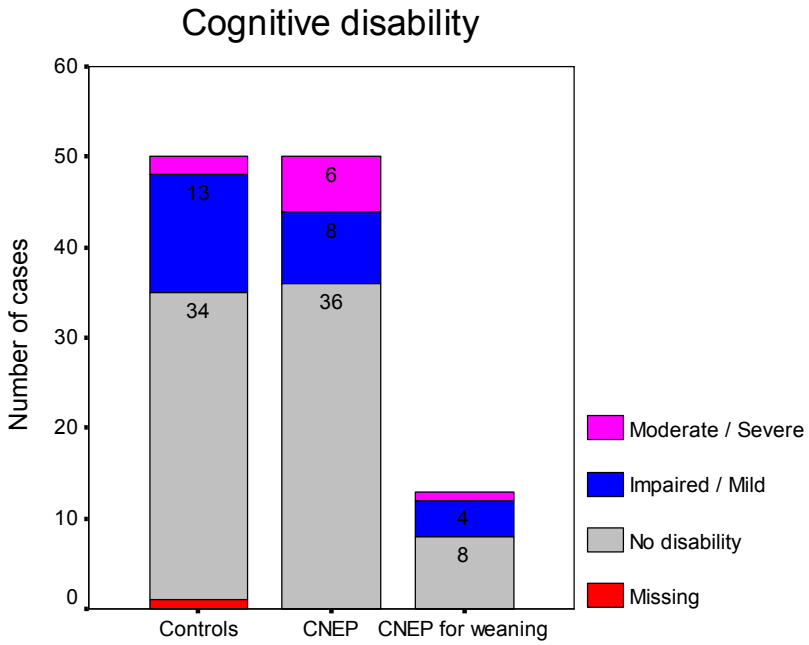

Figure 25: Stacked bar graph of cognitive disability; no significant difference was found between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

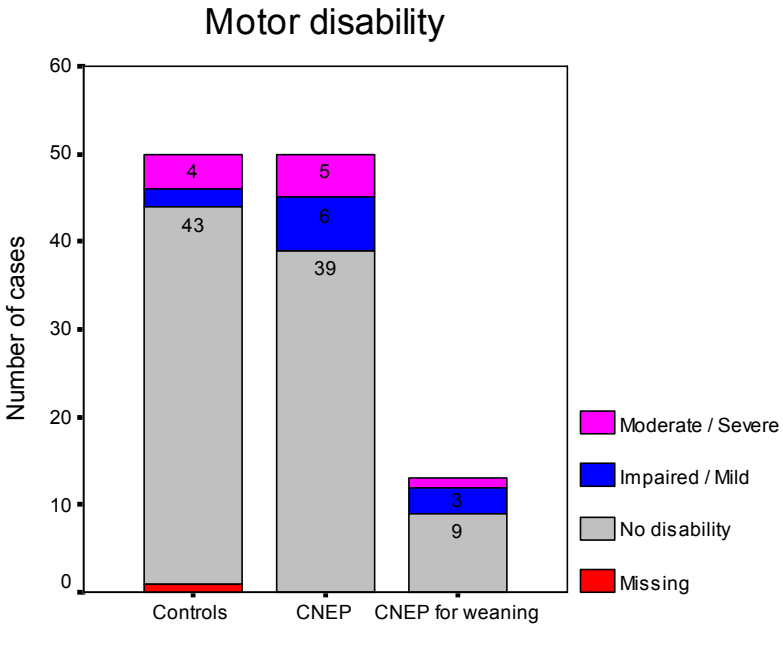

Figure 26: Stacked bar graph of motor disability; no significant difference was found between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

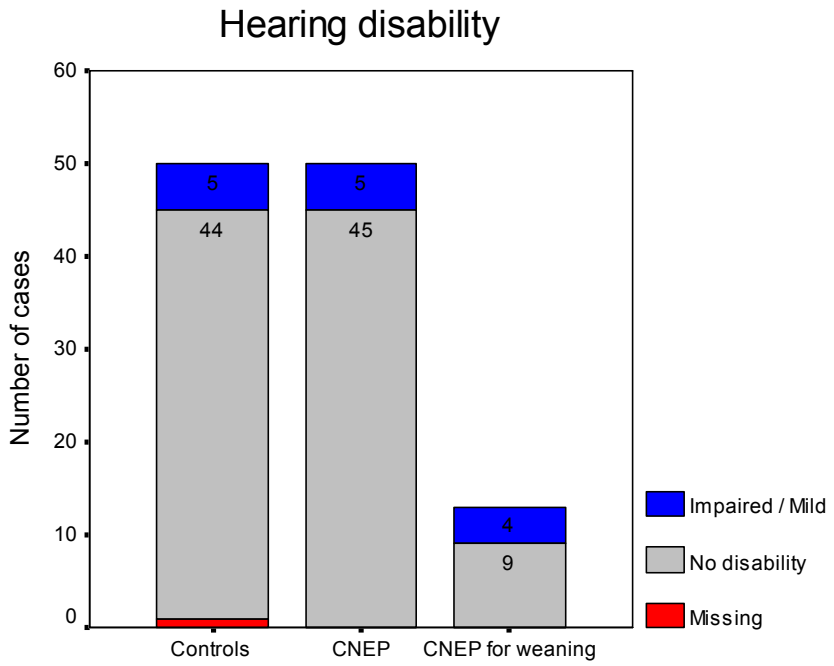

Figure 27: Stacked bar graph of hearing disability; no significant difference was found between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

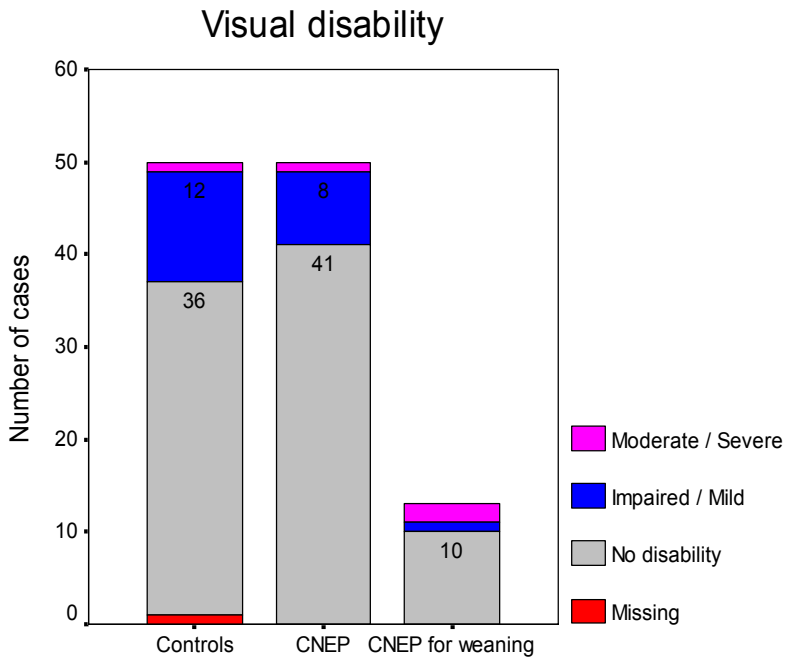

Figure 28: Stacked bar graph of visual disability; no significant difference was found between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

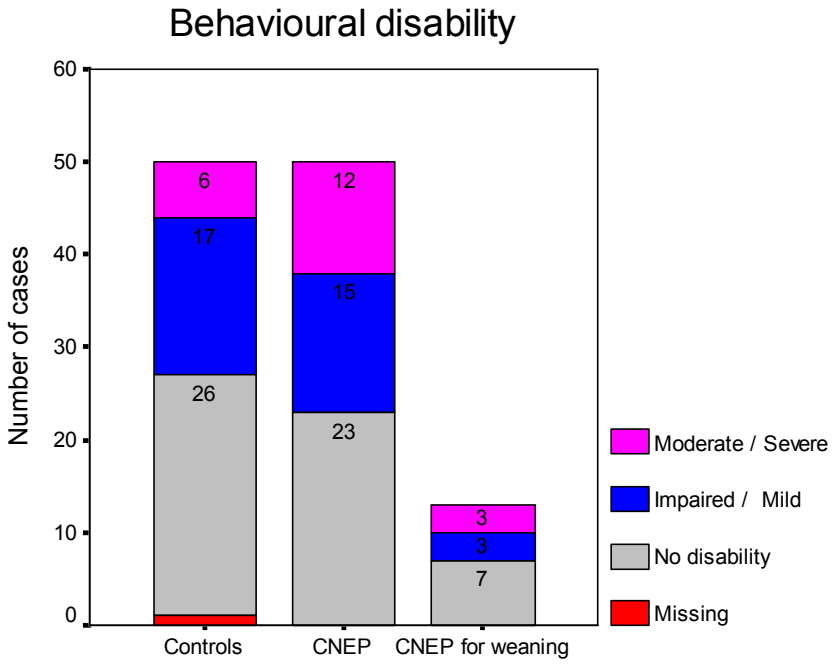

Figure 29: Stacked bar graph of behavioural disability; no significant difference was found between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

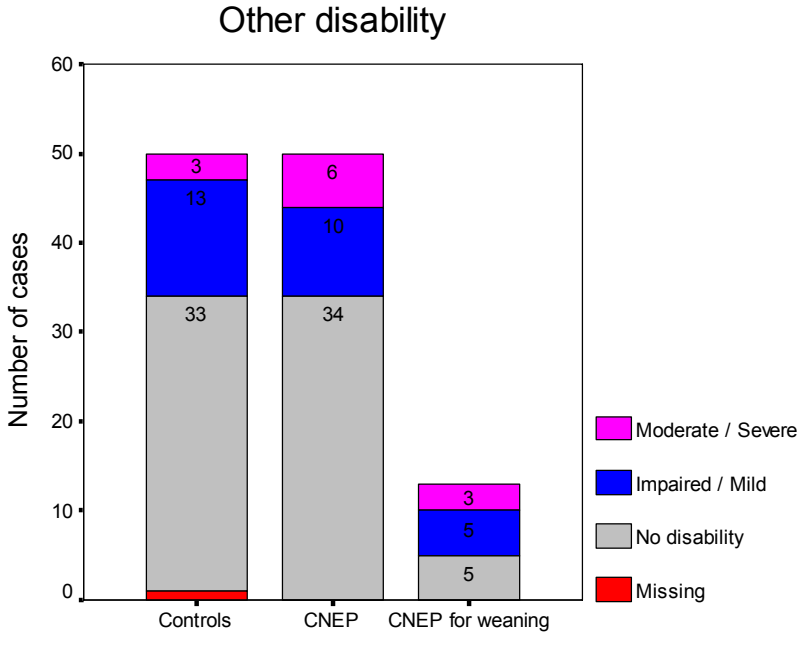

Figure 30: Stacked bar graph of other disability; no significant difference was found between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

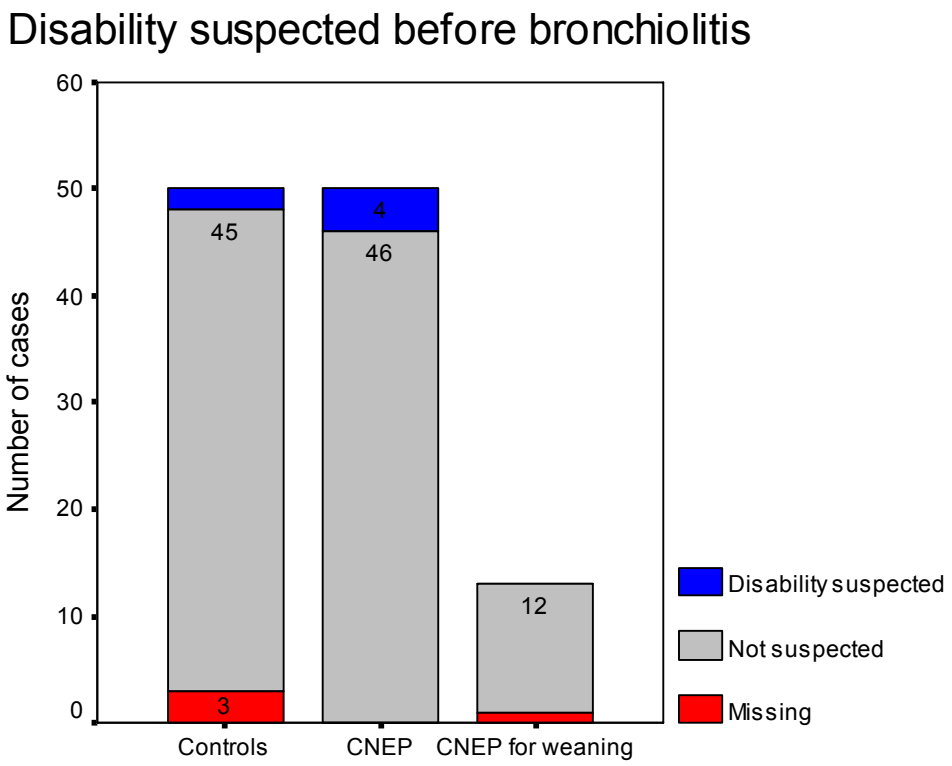

Figure 31: Stacked bar graph showing whether or not a diagnosis associated with disability was suspected before admission with bronchiolitis; no significant difference was found between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

Table 22: Known or suspected diagnoses associated with disability in children in the CNEP and control cohorts at the time of assessment

	CNEP	Controls
Down Syndrome	2	1
Haemorrhagic hydrocephalus	1	0
Severe learning difficulties	1	0
Suspected Cornelia De Lange	1	0
Peter's Plus Syndrome	0	1
Cerebral Palsy	1	2

5.1.4.5 Parent reported health related quality of life

This was assessed using the HUI3 multi-attribute scores. The median HUI score for the CNEP group was 1.00 (IQR: 0.85 -1.00) and did not differ significantly from that of the controls 0.99 (IQR: 0.81 -1.00), n=48 pairs; p=0.37 (Figure 32).

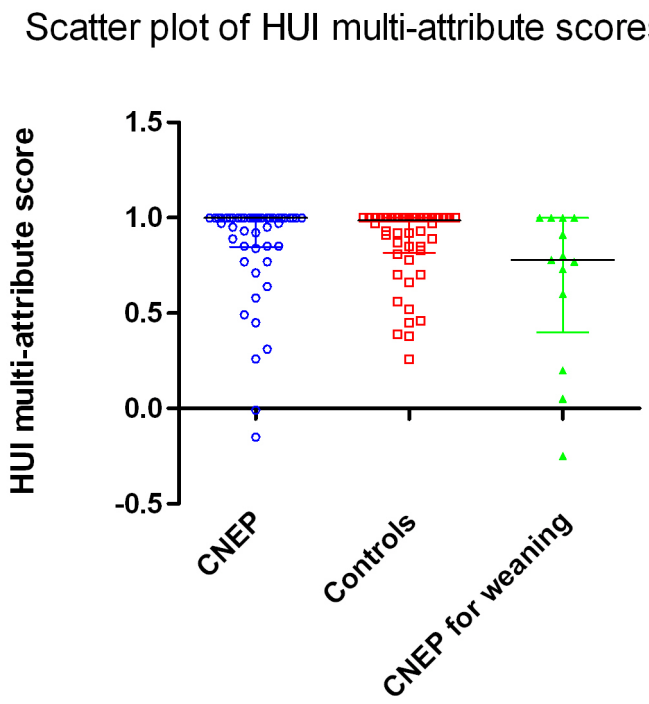

Figure 32: Scatter plot of the Health Utilities Index 3 multi-attribute scores showing no significant difference between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

5.1.4.6 Growth measures

The CNEP group were heavier and taller than controls although this was not statistically significant. Median weight z-score was 0.53 (Range -2.79 to 3.13) for the CNEP cohort [n=50] and -0.02 (Range -3.96 to 3.39) for controls [n=49]. The median height z-score was 0.02 (Range -3.14 to 2.10) for the CNEP cohort [n=50] and -0.09 (Range -4.66 to 1.77) for controls [n=49]. The median head circumference z-score was 0.53 (Range - 5.9 to 3.53) for the CNEP cohort [n=50] and -0.36 (Range -3.9 to 2.74) for controls [n=48]. A child in the 'CNEP for weaning' group had a rare syndrome which resulted in profound growth restriction ('CINCA Syndrome'). The data for this child are included as they are true measurements. Weight, height and head circumference z-scores are depicted in Figures 33-35.

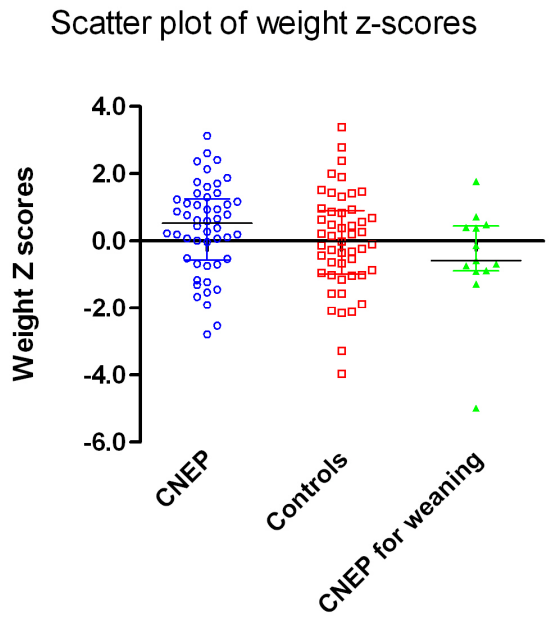

Figure 33 : Scatter plot of weight z-scores showing no significant difference between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group.

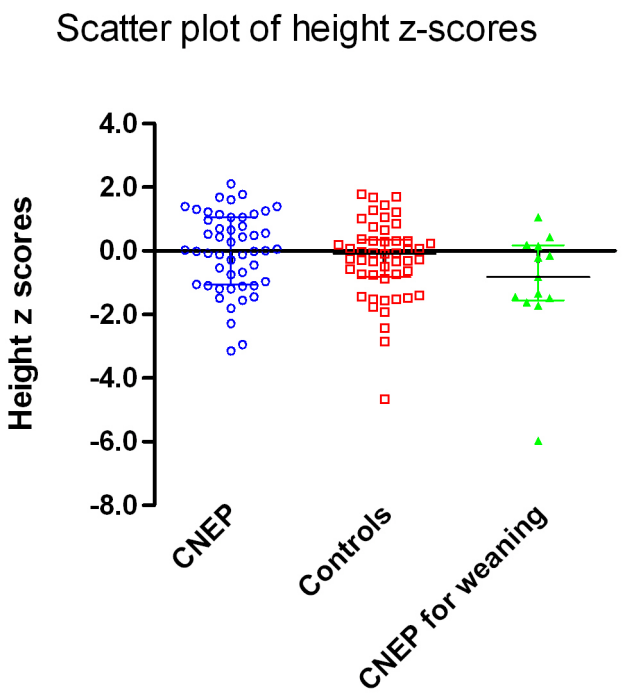

Figure 34: Scatter plot of height z-scores showing no significant difference between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group

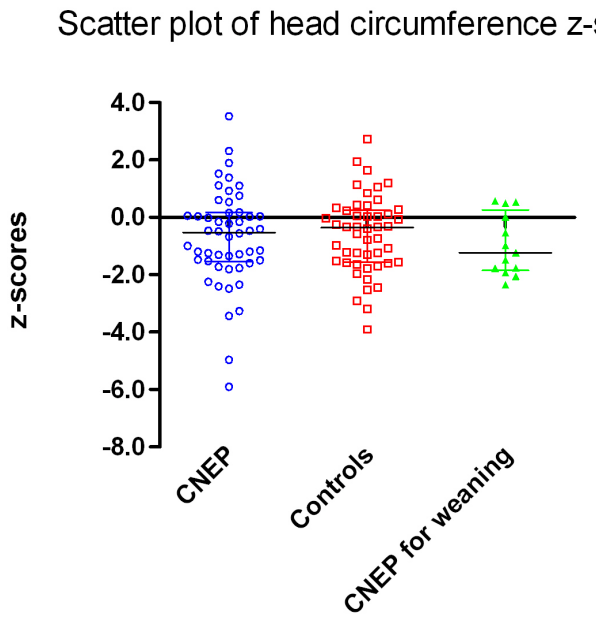

Figure 35: Scatter plot of head circumference z-scores showing no significant difference between the CNEP cohort and their controls. Data for the children who received 'CNEP for weaning' are displayed without a comparison group

5.2 Uncontrolled study of CNEP used to facilitate weaning from PPV

The data of 13 children who had PPV as their primary treatment but received CNEP to help aid weaning from respiratory support are provided in this section. These children were identified as a group that needed separate evaluation to those in whom CNEP was the primary treatment. No suitable control group was identified for these children; however, data obtained from their evaluation has been included in this thesis for completeness and to allow any important trends or patterns to be identified. Without a control group it is not possible to determine the effect of either treatment modality (CNEP and PPV) on the outcome measures evaluated as both modalities could be contributing to the measurement being investigated. Analysis of the data obtained from this group is limited to descriptive statistics and general comparisons with the CNEP and control groups. Data have also been illustrated graphically in Figures 9-35 alongside those of the children evaluated as part of the matched cohort study and listed separately in Tables 23-29.

5.2.1 Matching criteria

Children who received CNEP for weaning from PPV were evaluated against matching criteria (Table 13) to determine how this group differs from children evaluated in the matched cohort study. There were fewer males (39%) and they had significantly higher pre-ventilation FiO_2 (0.48) compared to the CNEP group (p=0.012) but not the controls (p=0.32). There was also a trend towards more severe illness in this

group (Table 13) compared to those in the matched cohort study (χ^2; p=0.06). Their median gestational age was 36 weeks and 85% were RSV positive, both similar to the other groups. Their median age at study evaluation was 6.7 years, which was not significantly different to the CNEP group but was younger than the controls.

5.2.2 Demographic and neonatal variables

Demographic data for the children who received 'CNEP for weaning' are listed in Table 23 and are similar to those of children in the matched cohort study.

Table 23: Demographic information of children who received CNEP for weaning from PPV

	Mean [n]
Mean birth weight (grams)	2450 [13]
Mean maternal age (years)	36.7 [13]
Mean paternal age (years)	36.2 [11]
[a]Overcrowding index	1.00 [12]
Maternal social class	
Non-manual	7[13]
Manual	6[13]
Paternal social class	
Non-manual	6[10]
Manual	4[10]
Current smokers in household	8 [13]
Maternal smoking in pregnancy	5 [12]
Receiving benefits	8 [13]

None of the children who received CNEP for weaning from PPV were intubated at birth. The neonatal data of these children is otherwise similar to those of the children in the matched cohort group (Table 24).

Table 24: Neonatal information of children who received CNEP for weaning from PPV

	Frequency [n]
NICU admission	8 [13]
Intubated at birth	0 [12]
Ventilated in NICU	2 [13]
Intraventricular haemorrhage	1 [11]
Postnatal steroids for chronic lung disease	0 [11]
Neurological abnormality suspected at birth	0 [12]
	Median (Range) [n]
Median number of days ventilated (NICU)	0 (0 -11) [13]
Median number of days in 0_2 (NICU)	0 (0 -154) [12]

5.2.3 Outcome evaluations

Lung function results of children who received CNEP for weaning from PPV are listed in Table 25. These results do not differ significantly from those of children in the CNEP or control cohorts.

Table 25: Lung function tests of children who received CNEP for weaning from PPV

		Median values [n=11]	Range
Baseline Airway Resistance	($kPaL^{-1}s^{-1}$)	0.80 [12]	0.4 to 2.45
	(% predicted)	103.0	65.0 to 137.0
Airway Resistance post bronchodilator	($kPaL^{-1}s^{-1}$)	0.49	0.3 to 1.57
	(% predicted)	62.0	44.0 to 161.0
% change in Airway Resistance		-29.5	-56.0 to 20.0
FEV_1	(% predicted)	87.1	56.6 to 110.1
FEV_1 post bronchodilator	(% predicted)	97.2	59.8 to 120.0
% change in FEV_1		6.2	-2.2 to 40.1
FVC	(% predicted)	91.2	63.4 to 119.1
FVC post bronchodilator	(% predicted)	103.5	62.0 to 120.9
% change in FVC		2.0	-5.0 to 18.7
FEF_{25-75}	(% predicted)	82.7	48.3 to 117.3
FEF_{25-75} post bronchodilator	(% predicted)	101.4	69.9 to 132.8
% change in FEF_{25-75}		15.5	-6.6 to 109.9

Parent reported respiratory outcomes in children receiving CNEP for weaning are listed in Table 26. There are no major differences in these measures when compared to CNEP or control cohorts other than the frequency of wheezing which was more likely to be moderate or frequent than the other two groups.

Table 26: Respiratory outcomes reported by parents for children who received CNEP for weaning from PPV

	Frequency [n=13]
Any wheezing in previous 12 months	8
Ever diagnosed asthma	7
Follow up by a paediatrician for respiratory disorder	4
Current use of bronchodilators	8
Current use of steroid inhalers	6
Frequency of wheeze in previous 12 months	
No wheeze	5
Occasional wheeze (1-3 episodes)	1
Moderate wheeze (4 -12 episodes)	5
Frequent wheeze (> 12 episodes)	2
No. of extrinsic*factors	[n=12]
None	4
1	6
2	0
3	2
No. of intrinsic† factors	[n=13]
None	2
1	2
2	4
≥3	5
	Mean [n=13]
No of days off school with respiratory illness	8.2
No of days off school with any illness	13.9

*Extrinsic factors = Damp, mould, long haired or feathered pets †Intrinsic factors = Family history of asthma or wheezing, hay fever or chronic chest problem.

There were no major differences in the prevalence of disability in children receiving CNEP for weaning compared to the CNEP cohort or controls (Table 27 and 28). The health related quality of life assessed with the health utilities index 3 multi-attribute score does not differ significantly from that of children in the CNEP and control cohorts (median HUI score 0.78 IQR: 0.40 - 1.00).

Table 27: Disability within 6 domains in children who received CNEP for weaning from PPV

	Frequency [n=13]
Moderate or severe cognitive disability	1
Moderate or severe neuromotor disability	1
Moderate or severe visual disability	2
Moderate or severe hearing disability	0
Moderate or severe behaviour disability	3
Moderate or severe other disability	3
Any moderate or severe disability	6
Any moderate or severe disability (excluding behaviour)	4

Table 28: Worst disability in children who received CNEP for weaning from PPV

	Worst disability	Worst disability (excluding behaviour)
No disability	4	4
Impaired / mild	3	5
Moderate / severe	6	4

5.2.3.1 Short term outcome measures

Short term outcome measures are shown in Table 29. Children in whom CNEP was used for weaning spent longer ventilated overall and were admitted to PICU for longer periods than children in both the CNEP and control cohorts ($p=0.005$ and $p<0.001$ respectively). They

also spent significantly longer receiving oxygen therapy (p=0.003) and in hospital (p=0.001) than children in the control groups (Figures 18 and 19).

Table 29: Bronchiolitis illness variables in children who received CNEP for weaning from PPV

		Range	[n]
Median length of stay on PICU (days)	6	(4 -28)	[13]
Median length of stay in hospital with bronchiolitis (days)	15	(7-37)	[11]
Median duration of 0_2 therapy with bronchiolitis illness (days)	11	(6-32)	[9]
Median duration of nasogastric or intravenous feeding (days)	8	(3 - 32)	[13]
Median duration of IPPV/ CPAP	4	(1 -24)	[13]
Median time from admission to hospital to ventilation (hours)	7	(0-119)	[10]
Median duration of CNEP (days)	3	(1- 9)	[13]

5.2.3.2 Growth measures

Children in whom CNEP was used for weaning were shorter and lighter than children in the CNEP cohort but not the controls. The median weight z-score was -0.58 (range -4.99 to 1.77) and the median height z-score was -0.83 (range -5.97 to 1.06). The median head circumference z-score was -1.23 (range -2.35 to 0.57) and not significantly different to the other two groups (Figures 33-35).

6 Discussion

6.1 Summary of findings

The study aim was to determine whether there are respiratory or neurological consequences to the use of CNEP for the treatment of bronchiolitis. The primary hypothesis was that there is no difference in airway resistance measured in later childhood between infants who received CNEP for bronchiolitis and matched controls. The secondary hypotheses were that there were short term benefits associated with the use of CNEP but no difference in respiratory symptoms, disability or health related quality of life in children receiving this treatment compared to controls treated with conventional methods. The findings from this study do not support the primary hypothesis and instead show significantly increased airway resistance in children treated with CNEP when assessed at a median age of 6.4 years. The forced mid-expiratory flow (FEF_{25-75}) was also significantly lower in children treated with CNEP in keeping with the finding of increased airway resistance. There were no differences in any of the other spirometric measures, including FEV_1 and FVC, and no difference in the frequency of reported respiratory symptoms such as wheeze. Disability (defined in Table 11) and health related quality of life assessed with the Health Utilities Index were not significantly different between the groups.

The finding of a significant difference in airway resistance raises a number of questions including:

1. If CNEP is associated with higher airway resistance is the difference observed of any clinical significance?

2. Are there factors other than the mode of respiratory support received which differ between the groups and contribute to the difference in airway resistance?

3. If the use of CNEP is truly associated with higher airway resistance, what is the mechanism involved?

6.2 Difference in airway resistance

In the next sections I will discuss potential confounding factors and other possible explanations for the difference in airway resistance observed. These will be considered under the headings: “is the difference of clinical significance?”; “population differences” and “effect of CNEP on airway resistance”.

6.2.1 Is the difference of clinical significance?

Although the difference in baseline *R*int between the groups is statistically significant it is important to ascertain if it has clinical significance. *R*int has

been shown to have a high coefficient of variability particularly in children with RAD (Chan et al., 2003). The within-occasion variability of *R*int in a healthy individual is of the order of 20% and is much higher than that of other spirometric measurements. In an individual, a change in *R*int of this magnitude between 2 measurements taken on the same occasion may therefore reflect natural variability. For the comparison of 2 groups, however, this difference still has clinical significance as the co-efficient of variability relates to an individual and not a group. A randomised controlled crossover trial of the use of fluticasone in preschool children with intermittent wheeze found a mean reduction in *R*int of 16% after 6 weeks of treatment in children sensitised to aeroallergens. The mean *R*int returned to baseline 16 weeks after stopping treatment. The difference in median *R*int observed in this study of 16.5% is of a similar magnitude and must also be considered clinically significant. However, this degree of change in *R*int is comparable to a difference in FEV_1 of less than 5% which is only a small change in respiratory function. In a randomised study of the effects of anti-asthma treatment on lung function in children, Stelmach et al. (2007) evaluated 150 children with a range of lung function tests following treatment with budesonide, montelukast, budesonide + formoterol, budesonide + montelukast or placebo. The lung function tests included the spirometric measures: FEV_1 and FEF_{25-75}; specific airway resistance measured using plethysmography (SRaw) and *R*int. All four measures were tested in the 5 groups before and after 4

weeks of active treatment or placebo. *R*int, SRaw, and FEV_1 improved significantly in all active treatment groups, whilst FEF_{25-75} only increased significantly in the 2 groups treated with montelukast and budesonide + montelukast. A change in *R*int of 18-20% corresponded to a change in FEV_1 of 5% and a change in FEF_{25-75} of 8%. Interestingly, *R*int performed better than SRaw in discriminating responses to treatment, confirming the view that it is a sensitive tool for assessing airway reactivity. The lack of a significant difference in other spirometric measures such as FEV_1 and FVC or in other clinical outcome measures, suggests the difference found in baseline *R*int between the CNEP and control groups represents a small difference in respiratory function. It is, however, of sufficient significance to require a plausible explanation.

6.2.2 Population differences

Differing degrees of prenatal or environmental cigarette smoke exposure could account for some of the observed difference in airway resistance between the groups. Kooi et al. (2004) evaluated the effect of parental smoking on *R*int measurements in 557 children aged 4 -12 years and found that *R*int values were 7% higher in children (n=84) who had 1 or 2 parents smoking ≥ 3 cigarettes/ day in their presence, compared to those of children (n= 473) whose parents smoked less or not at all. In a subgroup of 180 pre-school children aged 4-6 years, the mean *R*int values

were 13% higher in the children exposed to cigarette smoke (n=20) compared to those in children (n=160) exposed to none.

There was a trend towards increased reporting of maternal smoking in pregnancy in the CNEP group in this study (23 CNEP, 14 Controls; p=0.07) and a higher proportion of parents of CNEP children smoked at home although the difference was not significant (28 CNEP, 19 controls; p=0.17). Despite the lack of significance in the difference in reported smoking, it remains possible that the degree of cigarette exposure was further different between the groups as the numbers of cigarettes smoked by parents was not quantified but could well have differed.

Another potential confounder was the use of inhaled corticosteroids. Eleven control children were prescribed inhaled steroids compared with 7 from the CNEP-treated group, which is not statistically significant (p = 0.32). However, the drug dose, effectiveness of technique and compliance have not been assessed and so it is not possible to say with confidence whether one group received more inhaled steroid than the other; published data by Nielsen and Bisgaard (2000) suggest this may be important. The authors conducted a randomised placebo-controlled study of inhaled budesonide 400 micrograms twice daily in 38 children (19 cases, 19 controls) aged 2-5 years with asthma. There were no significant

differences in passive smoking exposure or atopic disposition between the groups and baseline *R*int values were not significantly different; after 8 weeks, however, the budesonide-treated group had significantly lower *R*int values (median 1.10 $kPa.L^{-1}.s^{-1}$ [95% C.I. 0.98 -1.22]), compared with controls (1.26 $kPa.L^{-1}.s^{-1}$ [95% C.I. 1.14 -1.38]; p=0.01).

Children were not specifically matched for age but this was indirectly controlled for by selecting controls from a cohort of children treated at a similar time to the CNEP group. Seventy six percent of controls were matched within an age range of +/-2 years of their CNEP pair and 88% were within +/- 3 years (Range -3.76 to + 4.87 years). The median age of children treated with CNEP was 6.4 years and the median age of controls was 7.7 years. The potential effect of this age difference is highlighted by the Tuscon Children's study which evaluated the incidence of reactive airway disease (RAD) in an original cohort of 207 children with RSV lower respiratory tract illness at 3, 6, 11 and 13 years (Stein et al., 1999). The authors showed that the prevalence of RAD declined steadily until children were aged 13 years when it was similar to that of the background population. The effect of this decline in prevalence of RAD on a cohort of children following bronchiolitis is that older children will have less RAD than younger ones. The controls were on average 1.3 years older than children in the CNEP cohort by the time they were assessed due to slower

recruitment to this group resulting in later assessments. Percentage predicted *R*int values have been used to allow for any difference in age when comparing airway resistance in children of different of ages- however, this simply allows for age related changes in *R*int in a healthy population and does not take account of the changing prevalence of RAD over time. The older age of controls may therefore have an effect on their airway resistance measurements, reflecting a declining prevalence of RAD with time.

Apart from the older age of controls, no other population variables differed significantly between the groups; however, a few measures have been identified (prenatal or current parental smoking and prescription of inhaled corticosteroids) which differed in controls compared with the CNEP cohort in ways that would favour a lower *R*int value. It is conceivable that the collective effects of these variables could have contributed to a significantly lower Rint measurement.

Children in the CNEP cohort were well matched with controls for all the matching criteria except the median pre-ventilation FiO_2, which was 12% higher among the controls. Seventy two percent of subjects were matched within a FiO_2 range of +/-10% and 18% within +/-15% but in the remaining 10% the matching was only possible within a FiO_2 range of +/-21%. This

reflects the fact that 54% of children in the CNEP group were receiving nasal cannula oxygen at rates of 0.5-2.5 litres/ minute when intervention was deemed necessary, because of recurrent apnoea or because clinicians believed they were 'tiring'. This compares with just 14% of controls receiving nasal cannula oxygen at rates of 0.5-2 litres/ minute. Apnoea was recorded as the reason for starting respiratory support in 7 children treated with CNEP and in 5 controls. Matching children in the CNEP group with controls receiving similarly low oxygen concentrations may have resulted in CNEP cases being paired with controls with a less severe illness, as the matching criteria did not take account of measures of type II respiratory failure. An alternative explanation is that intervention with respiratory support in the CNEP group was at an earlier stage than it was in the control group, resulting in a longer period of exposure to the unwanted effects of ventilatory support. Matching was done on the basis of FiO_2 irrespective of whether controls received respiratory support or not, because published data from NSH indicates that CNEP was started early in some cases with the aim of avoiding later intubation. In the study by Hartmann et al. (1994b) indications for starting CNEP included any infant with bronchiolitis requiring $FiO_2 \geq 0.4$, so it is likely that some children treated with CNEP who are included in this study would not, in other centres, have received any respiratory support.

Recognised features of respiratory failure and indications for respiratory support include: signs of clinical deterioration (see below), hypercarbia ($pCO2 \geq 8.0$ kPa) with or without respiratory acidosis, persistent hypoxia ($paO2 \leq 8.0$ kPa despite $FiO_2 \geq 40\%$), metabolic acidosis, apnoea or bradycardia (Outwater and Crone, 1984). Clinical deterioration is judged by worsening respiratory distress (defined as severe recession, hyperinflation, diminished breath sounds, increasing tachypnoea or tachycardia), heart rate > 200 beats per minute, listlessness or impaired peripheral perfusion. It was not possible, from a retrospective review of medical notes, to assess reliably for clinical deterioration but one or more of the remaining criteria for respiratory support (i.e. hypercarbia, hypoxia despite $FiO_2 \geq 40\%$, metabolic acidosis, apnoea or bradycardia) were met by 33 children treated with CNEP and 27 controls. Of the 27 matched controls with signs of respiratory failure, 18 received IPPV, 4 were admitted to PICU but managed conservatively and 5 were managed conservatively on a general paediatric ward. Twenty six CNEP cases and 23 controls were admitted to PICU. The similar numbers of children in each group with respiratory failure or requiring PICU admission suggest that appropriate matching for illness severity was achieved.

6.2.3 Effect of CNEP on airway resistance

Another theoretical explanation for the observed difference in airway resistance between children treated with CNEP and controls might be the differing effects of ventilator associated lung injury on each group. Negative pressure ventilation could theoretically be associated with lung injury in a similar way to positive pressure ventilation by causing alveolar overdistension (volutrauma) (Slutsky, 1999). Positive pressure ventilation in neonates with respiratory distress syndrome has been reported to be associated with subsequent increase in airway resistance (Stocks and Godfrey, 1976). Fourteen of the 50 children (28%) treated with CNEP also received intermittent negative pressure ventilation (with pressures up to –30 cm H_2O). Because the volutrauma effects of PPV and NPV are likely to be similar, one might surmise that lung function abnormalities, including airway resistance, observed after PPV may also occur after treatment with NPV- however, there are no reported studies investigating this hypothesis to the author's knowledge. Therefore the observed difference in airway resistance between the groups may result from the differing numbers of children receiving ventilatory support in each group. Half of the control group in this study received no ventilatory support and so fewer controls would have been exposed to the effects of ventilator associated lung injury compared to the CNEP treated group. To the author's knowledge there are no long term studies comparing lung function measures in children previously treated for bronchiolitis with or without ventilation.

6.3 CNEP used for weaning from PPV

Children who received CNEP for the purpose of weaning from PPV were evaluated in addition to those who received CNEP as primary treatment, in view of recommendations made in the Griffiths report that all children who received CNEP were assessed for evidence of significant benefit or harm. Unlike the group who received CNEP as primary treatment, a suitable control group could not be identified for this group of children thereby limiting the interpretation of the data obtained. Although the data on these children have been depicted graphically alongside those of children in the matched cohort study, the 'CNEP for weaning' group is not directly comparable to either the CNEP or control cohorts. These children were either deemed to be so unwell at presentation to NSH that they required immediate intubation and ventilation or they were transferred from another centre to NSH already receiving PPV. In both cases they only received CNEP in the recovery phase of their illness to speed up the process of weaning from PPV. As a group they are likely to represent children with a more severe illness than those recruited to the matched cohort study; this is evident by the matching criteria showing that all of these children had a severe bronchiolitis illness at presentation compared to 78% of children in the CNEP and control cohorts. The outcome measures evaluated in this study are likely to have been influenced as much (if not more) by the positive pressure ventilation as the negative pressure support which these children received. The closest available comparison group to the children

who received ‘CNEP for weaning’ is a subgroup of the control cohort who received PPV (n=17). These children would not have been matched by any of the stipulated criteria. However, no significant difference was found in any of the primary or secondary outcome measures in a comparison of the two groups (i.e. ‘CNEP for weaning group’ and ‘children in the control cohort who received PPV’).

6.4 Comparison with published work

6.4.1 Respiratory outcome after bronchiolitis

Parents in this study reported ‘current wheeze’ (wheezing in the previous 12 months) in 30% of children treated with CNEP and 27% of controls; this is similar to that reported by Noble et al. (1997) who found wheeze in 34% of a cohort of 61 children assessed 10 years after bronchiolitis. Murray et al., (1992) found current wheeze in 42.5% [n=73] of the same cohort assessed by Noble et al. when they were assessed at 5½ years. Parent reports of children who had ever been diagnosed with asthma was 36% in those treated with CNEP and 39% in controls and is in keeping with the findings of previous studies reporting ‘any wheeze’ (wheezing at any time following the bronchiolitic illness) (Pullan and Hey, 1982, Mok and Simpson, 1984).

Mean FEV_1 values of 90.7% and 91% were reported by Mok and Simpson (1984) and Noble et al. (1997) respectively in cohort studies of children following bronchiolitis. Similar measurements were obtained in children in this study: median FEV_1 was 86.3% in the CNEP group and 88.5% in the controls. Mok and Simpson (1984) reported a mean FEF_{25-75} value of 89.1% in a cohort of 102 children evaluated at a mean age of 7 years following bronchiolitis. This finding is similar to the median FEF_{25-75} measurement of 86.8% found in the controls in this study. Significantly lower median measurements of 77.5% were obtained in the CNEP group, reasons for which are unclear. It is likely that the lower median FEF_{25-75} measurement in the CNEP group is caused by the same factor(s) resulting in a significantly lower *R*int measurement in this group as both are affected by small airways disease; possible reasons for this have been discussed earlier. A bronchodilator response ratio (BDR) > 1.22 was found to be associated with previous 'doctor confirmed recurrent wheezing' in a study of 82 children with recurrent wheeze and 48 with no symptoms with 76% sensitivity and 80% specificity (McKenzie et al., 2000). Baseline *R*int > 1.45 $kPa.L^{-1}.s^{-1}$ likewise had 80% specificity but only 60% sensitivity. Thirty three children (75%) treated with CNEP and 31 controls (67%) able to perform Rint measurements had a BDR ≥ 1.22. This measure has not previously been reported in cohort studies of children treated for bronchiolitis to the author's knowledge.

6.4.2 The use of CNEP for bronchiolitis

Previous studies of the use of CNEP for bronchiolitis have tended to be uncontrolled trials involving small numbers of children (Samuels and Southall, 1989, Linney et al., 1997). There are two reported controlled trials one of which was published in abstract form only (Hartmann et al., 1994b). The other controlled study by Al-balkhi et al. (2005) was a retrospective review of hospital case-notes and unlike this study did not involve any clinical assessments. The limited evidence from all of these studies suggests that the use of CNEP may reduce the need for intubation in children with bronchiolitis associated respiratory failure. The study by Al-balkhi et al. (2005) found no difference in the duration of oxygen therapy but observed a reduced duration of intensive care stay in children treated with CNEP. A possible confounding factor in the study was the trend towards an increased use of methylxanthines in the CNEP group (17 treated with NPV vs 6 in the standard group; p=0.06). Historically, methylxanthines were used more commonly for the purpose of reducing bronchiolitis related apnoea despite limited data to support its use (Ramesh and Samuels, 2005). Methylxanthines are rarely used in bronchiolitis now with clinicians tending to use CPAP more readily for such children. A randomised trial is currently underway to evaluate the role of aminophylline in reducing the need for respiratory support in severe bronchiolitis (Royal Children's Hospital Website).

This study supports the findings of others in showing a reduced need for intubation in the CNEP cohort but found duration of oxygen therapy to be increased and no difference in the mean length of stay in hospital or intensive care.

6.4.3 Disability and functional outcome following bronchiolitis

Disability and functional outcome are rarely reported following bronchiolitis; only two uncontrolled studies have been identified which report on this (Wren et al., 1982, Bray and Morrell, 1982). This outcome is, nevertheless, of particular concern to some parents whose children were treated with CNEP and was one of the main reasons for the recommendation that its use was discontinued pending further evaluation of the children who had been treated with it. Concerns about the possible risks of IVH associated with CNEP were suggested by Cvetnic et al. (1990) who noted that 4 infants with IVH had extensions of the bleeding after treatment with CNEP, leading the authors to recommend its use was avoided in babies most at risk of IVH. Further concerns about adverse neurological outcome following CNEP have stemmed from the randomised study of its use in preterm neonates by Samuels et al. (1996) which found a non-significant difference in the frequency of intraventricular haemorrhage (IVH) and death in a group treated with CNEP compared to controls. One of the concerns associated with earlier models of the CNEP

tank was the possible effect of the neck seal in obstructing jugular venous drainage. This concern was addressed with the use of a latex neck seal in the newer model of CNEP tank, following work reported by Palmer et al. (1994) which found no significant effects on jugular venous drainage.

In a recent follow-up study by Telford et al. (2006) of children treated in the original randomised trial of CNEP for neonatal RDS, a careful evaluation was conducted of survivors for any evidence of adverse neurological outcome. The primary outcome of death or severe disability did not differ significantly between the CNEP and control groups and no evidence was found of adverse outcome on detailed assessment of cognition, neuropsychological function; behaviour and health related quality of life. The findings of this study are in keeping with those of Telford et al. (2006) in that no significant difference was found between CNEP treated children and controls in the prevalence of moderate or severe disability or in the parent reported health-related quality of life. Most children identified with a significant motor or cognitive disability in this study had a relevant diagnosis which was known before the admission with bronchiolitis. Two children in the CNEP group (1 haemorrhagic hydrocephalus, 1 cerebral palsy) and two in the control group (2 cerebral palsy) have been found to have significant neurological disorders following their admission with bronchiolitis. It is unclear whether predominantly perinatal factors or the

bronchiolitis illness have contributed to these diagnoses and it is clearly beyond the scope of this study to determine causation in any of these cases. A non-significant increase in the prevalence of moderate or severe cognitive disability amongst children in the CNEP cohort is explained by the higher prevalence of diagnoses associated with neurodisability, which were known before they were admitted with bronchiolitis. It would appear, therefore that the use of CNEP is not associated with an excess of major neurological diagnosis such as cerebral palsy in this study. Interestingly, parents own evaluation of their children's health related quality of life was remarkably similar in both cohorts with similar median Health Utility Index multi-attribute scores (CNEP 1.00, Controls 0.99; p=0.83).

An unexpectedly high prevalence of moderate or severe behavioural disability was observed in both the CNEP cohort (28%) and controls (20%). The 'Strength and Difficulties Questionnaire' which was used to assess this outcome is well validated and has a high degree of sensitivity for screening behavioural problems in children. Its limitation, however, is a low positive predictive value of 35% when completed by a single informant (Goodman, 2001). The positive predictive value may be improved by use of multi-informants i.e. parents and school teachers. The use of multi-informants was considered during the planning of the study design but deemed unnecessary because behavioural disability was to be assessed

as a secondary outcome measure and the testing done in a clinic setting. It is likely that the criteria for determining a moderate or severe disability based solely on parents' perceived impact of their child's behaviour problems (and not on convergence of parents and teacher's ratings) overestimates the degree of disability within this domain. In retrospect information provided by school teachers would have been helpful and potentially would have improved the reliability of these data.

6.5 Methodology of this study

6.5.1 Study strengths

This is one of only three reported controlled studies which have evaluated outcome following the use of CNEP in infants with bronchiolitis (including a study reported in abstract form only). It is the first to evaluate long-term outcome, with a median age at follow-up of 6.4 years and represents the largest cohort of children treated with CNEP for bronchiolitis. A prospective randomised study would be the ideal way to evaluate the use of CNEP for bronchiolitis, however, in view of some of the prevailing perceptions about its impact on later disability (Griffiths, 2003), it is most unlikely that it would be possible to recruit patients to such a study, even if ethical approval were granted, without a more thorough assessment of its safety first. A matched cohort design, on the other hand, allows a detailed evaluation of the previous experience with CNEP in infants with bronchiolitis, without exposing subjects to any potential harmful effects in

the process. Given the prevailing concerns, it is the most appropriate way to first evaluate this technique and to determine which outcome measures need to be considered in any future prospective controlled trial.

The study evaluates important respiratory outcomes which are known to occur frequently after bronchiolitis but is also the first to report specifically on disability and functional outcome measures after this illness. All other reports of these outcomes in cases of bronchiolitis have been case series and have not been evaluated in a systematic and controlled manner. The use of a combination of lung function testing and parent reported symptoms using a validated respiratory questionnaire has allowed for a detailed and objective assessment of respiratory outcome measures. Similarly, disability and functional outcome measures have been assessed objectively using validated questionnaires where available or disability criteria (based on WHO definitions) that are widely accepted.

Demographic and neonatal data were collected in sufficient detail to evaluate for possible confounding variables that may have biased the outcome measures in favour of one of the groups.

6.5.2 Study limitations

A major limitation of any retrospective matched cohort study is the difficulty achieving adequate matching of all the important variables. An important demonstration of this is to do with the matching of illness severity which was undertaken in this study with the use of bronchiolitis clinical criteria in conjunction with a measure of oxygen dependency instead of a more robust illness severity score. In a prospective study one could stipulate that an arterial pCO_2 measurement or 'PRISM' score was an essential inclusion criteria allowing for more reliable matching. Such data cannot obviously be obtained retrospectively if not collected systematically in a prospective manner. Equally, the measurement of a variable such as oxygen dependency can vary in respect to what target saturation one is aiming for. The target saturation can be clearly stipulated in a prospective trial but may have varied in a way that is not possible to ascertain when evaluated retrospectively. The effect of both of these examples would be to introduce bias or inadequate matching in a retrospective cohort study but could have been avoided in a prospective randomised study.

The relatively small number of subjects studied means this study lacks power to detect small differences in some of the secondary outcome measures. There were difficulties recruiting to both arms of the study with

just over 50% of children who received CNEP and eligible to be included agreeing to participate. Recruitment to retrospective cohort studies is generally recognised to be difficult, reported rates ranging between 40 and 97% (Rogers et al., 2004). Every attempt was made to maximise response rates by adopting measures shown to have an impact (Edwards et al., 2002). The measures used included carefully-worded invitation letters to avoid any ambiguity about the purpose for the study, reimbursement of travel costs, pre-paid stamped reply envelopes and up to 3 letters of invitation if the first brought no response. Another limitation of the small numbers and low percentage of potential subjects recruited (51% of the children receiving CNEP as primary treatment) is that the study findings may not be representative of all children treated with CNEP. Mean FiO_2 was not significantly different between children recruited to the study and those who were not, but children enrolled in the study were significantly more likely to have had severe bronchiolitis and so perhaps were more likely to suffer severe disability as a result (Bray and Morrell, 1982, Wren et al., 1982). The findings of this study are therefore likely to overestimate the prevalence of disability among all children treated with CNEP for a variety of conditions. The use of matched controls, however, has made it possible to ascertain if children with severe bronchiolitis treated with CNEP differ from children of similar illness severity who received standard treatment. Other parameters including frequency of RSV infection and

median gestation at birth were not significantly different between those recruited and those who were not.

The use of subjects from two different centres may have introduced bias despite the attempt to match subjects as closely as possible, due to differences in practice not identified or not measurable. It was not feasible to recruit controls from NSH because CNEP was used as standard treatment for all children requiring respiratory support with bronchiolitis.

The matched cohort design would usually require an increased number of controls to allow a 2:1 or 3:1 ratio of controls to index cases to improve reliability of the findings. However, within the pool of potential controls there were insufficient numbers in certain categories to allow any more than 1:1 matching e.g. gestational age < 32 weeks. It also proved difficult to recruit subjects to both arms of the study, particularly so to the control cohort which took considerably longer than recruitment of index cases adding to the impracticality of increased matching. Concerns about possible risks associated with CNEP may have served as an increased motivational factor for recruitment to the index cohort which was lacking in the controls. This phenomenon may have in itself introduced bias but every effort has been made to match the index cases and controls closely to avoid any such effect.

It was not possible to conduct a blinded study because, to aid recruitment and to minimise their travel costs, participating children had to be evaluated as close to their homes as possible, which in turn meant they were evaluated where they received their treatment for bronchiolitis. Thus children who received CNEP were evaluated in premises near to the NSH in Stoke on Trent, whilst the control children, who generally came from Nottingham, were assessed at QMC, thereby precluding the possibility of blinding.

The chosen primary outcome measure required minimal cooperation from subjects and the effect of the investigator on the measurement is likely to be minimal. Most other outcome measures evaluated were based on parent report and unlikely to be influenced by the investigator.

As discussed in section 6.2.1 above, the difference in median FiO_2 between the groups may suggest that matching for illness severity was not optimal. The use of a validated illness severity score such as the 'PRISM' would have minimised inconsistencies in matching, but this proved impossible because a previous audit of the medical notes of potential recruits to the study had revealed inconsistent recording of the data necessary for such scoring. Instead a pragmatic decision was made to match for illness severity using clinical criteria (Table 12), widely recorded

in UK paediatric units (Hodge and Chetcuti, 2000) as well as a measure of oxygen dependency. The FiO_2 pre-ventilation (FiO_2 pre-admission to PICU or maximum FiO_2 if not ventilated) was the chosen measure of oxygen dependency because it was recorded in all cases. There was no difference in bronchiolitis illness criteria between the groups (Table 13).

6.5.3 What could have been done differently?

The primary outcome measure was selected to assess whether the prevalence of RAD differs between children treated with CNEP and their matched controls. Airway resistance measured by the interrupter technique (*R*int) has recently become available and offers an opportunity to perform lung function tests on young children who would not normally be able to cooperate sufficiently with more standard tests such as spirometry or plethysmography; these are frequently used in association with a bronchial challenge or bronchodilator response to assess reactive airways disease. Two previous studies have used baseline *R*int as a primary outcome measure to evaluate the effect of inhaled corticosteroids in preschool children with asthma (Nielsen and Bisgaard, 2000, Pao and McKenzie, 2002). In the study by Pao and McKenzie (2002) baseline Rint and bronchodilator response ratios were both assessed as primary outcome measures and found to be significantly lower in the treatment group. Earlier studies which evaluated the repeatability of *R*int in healthy

children found acceptable ‘within subject’ coefficient of variability; 8.1% in a study by Klug and Bisgaard (1998). However, subsequent work in symptomatic children with cough or wheeze has found high variability (Chan et al. (2003). Baseline *R*int may therefore not be as useful for comparison of outcomes in children with possible reactive airways disease. The percentage change in *R*int or BDR, however, remains useful and has significantly less variability than the baseline *R*int.

Previous studies have found greater difficulty in recruitment if the study protocol included the administration of a drug; McKenzie et al. (2000) found that up to 25% of the recruits in their study refused a bronchodilator but were willing to perform baseline *R*int. In this study the percentage change in *R*int after a bronchodilator was evaluated as a secondary outcome measure and was achieved in 99% of the children who were able to undertake baseline Rint. An alternative measurement of RAD, the bronchodilator response ratio (BDR) characterised by the ratio of *R*int before and after bronchodilator, was also evaluated. *R*int was chosen primarily because it offered the opportunity to evaluate the prevalence of RAD objectively in the maximum number of children in the age range of 4-10 years. The successful testing of 92% of children recruited to the matched cohort study confirms this as an appropriate choice. However, in retrospect, the BDR rather than baseline Rint would have been a more

preferable choice as the primary outcome measure to compare the prevalence of RAD between the 2 groups. Both percentage change Rint and BDR were found to be not significantly different between the groups.

The data collected on the use of supplementary fluids was not recorded in sufficient detail to distinguish between the proportions of children in either cohort receiving nasogastric feeding as opposed to intravenous fluids. These data would be relevant for the reason that nasal obstruction is potentially more likely to occur with nasogastric feeding and if significantly different between the groups may be a confounding factor that has not been adequately evaluated (Sporik, 1994).

Earlier discussion about the possible overestimation of behavioural disability (section 6.4.3) highlights the fact that it would have been helpful to have included data on teacher responses to the 'strengths and difficulties' questionnaire in the study protocol, which was not obtained.

6.6 Implications for future research and use of CNEP for bronchiolitis

The results of this study suggest that the use of CNEP for bronchiolitis may be associated with a reduced need for endotracheal intubation and

has not been shown to be associated with an increased incidence of later respiratory symptoms or neurodisability. However, before CNEP is used routinely in the management of children with bronchiolitis there is a need to assess outcomes associated with its use more fully in a prospective randomised study. As well as assessing short term measures it will be important for any future studies to undertake longer term follow up to assess the later outcomes evaluated in this study. Areas that need particular focus are the possible advantages that CNEP use might have over standard treatment such as the reduced need for endotracheal intubation but also to assess whether this comes at the cost of a longer duration of oxygen therapy or hospital stay. It would be helpful to evaluate if CNEP has any advantages over CPAP which is currently the most commonly used mode of non-invasive respiratory support in children with bronchiolitis. In longer term follow up it would be especially important to assess later outcomes such as prevalence of respiratory symptoms, respiratory function and functional outcomes including assessments of disability and health related quality of life. A randomised study would hopefully reduce the likelihood of inappropriate matching of illness severity but given its importance it may be appropriate to stratify study groups to ensure this was adequately addressed.

7 Conclusions

This study was devised to determine if there are respiratory or neurological sequelae to the use of CNEP for bronchiolitis associated respiratory failure. This has been evaluated by assessing children who received CNEP at a median age of 6.4 years and comparing them with matched controls who received standard bronchiolitis treatment. Short term outcome measures have also been evaluated in the two groups. The findings of the study in relation to the study aim and the stated primary and secondary hypotheses have been reviewed and the conclusions that may be drawn from these findings are outlined below.

7.1 Primary hypothesis

The stated primary hypothesis was that: ***'There is no difference in airway resistance measured in later childhood between children who received CNEP for bronchiolitis and matched controls'***. The findings of this study suggest the primary hypothesis must be rejected as a significant difference was found in airway resistance when measured in later childhood. The reason for this difference, however, is most likely to be population differences which could not be adequately controlled for with the matched cohort study design. Another possible explanation is that PPV and CNEP have similar effects on airway resistance and that the difference in airways resistance observed is a reflection of the earlier use

and increased number of children receiving respiratory support in the CNEP group compared to the matched controls. It would seem unlikely that the observed difference reflects a specific adverse effect of CNEP on later airway resistance which is different to that observed with PPV, given the other possible causes identified which could explain the findings. However, the possibility of a specific adverse effect of CNEP on later airway resistance cannot be excluded.

The use of baseline *R*int as the primary outcome measure in this study has highlighted difficulties associated with interpretation of the measurements obtained when it is used to compare cohort groups. The secondary outcome measures of percentage change *R*int and bronchodilator response ratios (BDR) were not significantly different between the groups and provide a more reliable objective comparison of the prevalence of reactive airway disease in the CNEP and control groups.

7.2 Secondary hypotheses

The secondary hypotheses evaluated were as follows:

1) ***'The use of CNEP for bronchiolitis does not result in an increase in respiratory symptoms in later childhood compared with matched controls'***.

The findings from this study suggest this null hypothesis cannot be rejected as no significant difference was found in the frequency of wheezing episodes, in the numbers in whom asthma had been previously diagnosed and in the use of inhaled medication for reactive airways disease. There was also no difference in the reported number of days off school with a respiratory illness in the two groups.

2) ***'The use of CNEP during bronchiolitis is not associated with an increase in disability or worse health related quality of life among surviving children compared to controls'*.**

The study findings suggest this null hypothesis also cannot be rejected as no significant difference was found in the prevalence of disability defined using specific criteria. The wide confidence intervals, however, reflect the reduced power of this study to evaluate this hypothesis due partly to the fixed size of the original cohort and the difficulties encountered with recruitment. There was no significant difference in the health related quality of life assessed with the Health Utilities Index (HUI) multi-attribute score, a well validated measure for evaluating this outcome in the study population. The HUI findings could be considered to support those of the disability assessments as both measures evaluate similar domains of disability.

3) ***'The use of CNEP is associated with short-term benefit, such as a reduced need for intubation, when compared to controls'***.

This hypothesis was supported by the study findings in respect to the reduced need for endotracheal intubation and duration of PPV if ventilated, which were observed significantly less frequently or for a shorter duration respectively in the children treated with CNEP. Other short term outcome measures such as length of hospital stay were found to be no different in the CNEP and control cohorts and the duration of oxygen therapy was found to be increased in those treated with CNEP.

7.3 Summary

Bronchiolitis is the commonest cause of acute respiratory failure in infancy and results in several hundred admissions to UK paediatric intensive care units for respiratory support each year. Most children receive invasive PPV but non-invasive respiratory support is increasingly being used as more experience is gained in the newer non-invasive techniques. Non-invasive respiratory support is mostly provided with positive pressure devices and very little is known about the use of negative pressure respiratory support for children with bronchiolitis. A cohort of children treated with CNEP for bronchiolitis at a UK centre were the focus of a government enquiry which identified parental concern about the possibility that children receiving this treatment may have suffered significant harm. This study has been

conducted in an attempt to evaluate these concerns using a matched cohort design. Difficulties were encountered in recruitment, which meant that just over half of the original cohort agreed to participate in the study. Despite its limitations this is the only study to date to have evaluated longer term outcomes in children treated with CNEP for bronchiolitis and has provided new evidence to address the expressed concerns and stated benefits of its use for this illness. Careful evaluation of this cohort of children treated with CNEP has found no evidence to suggest that children receiving this treatment have suffered significant harm. The finding of higher airway resistance (*R*int) in the CNEP group although highly statistically significant, reflects a small clinical difference and is not associated with any increase in respiratory symptoms, need for medication, disability or parent reported quality of life. The higher *R*int in children treated with CNEP is most likely to reflect a difference in cigarette smoke exposure between the two groups. The study findings do suggest that the use of CNEP may be associated with a reduced need for intubation in children with bronchiolitis although it is unclear if it results in a longer duration of oxygen therapy and hospital stay. Further work is required to assess whether CNEP has advantages over other modes of non-invasive respiratory support for bronchiolitis (i.e. CPAP) and to evaluate the long and short term effects associated with its use more fully.

8 References

AHERNE, W., BIRD, T., COURT, S. D. M., GARDNER, P. S. & MCQUILLIN, J. (1970) Pathological changes in virus infections of the lower respiratory tract in children. *J Clin Pathol,* 23**,** 7-18.

AL-BALKHI, A., KLONIN, H., MARINAKI, K., SOUTHALL, D. P., THOMAS, D. A., JONES, P. & SAMUELS, M. P. (2005) Review of treatment of bronchiolitis related apnoea in two centres. *Arch Dis Child,* 90**,** 288-291.

ALEXANDER, G., GERHARDT, T. & BANCALARI, E. (1979) Hyaline membrane disease. Comparison of continuous negative pressure and nasal positive airway pressure in its treatment. *Am J Dis Child,* 133**,** 1156-1159.

ALLANDER, T., EMERSON, S. U., ENGLE, R. E., PURCELL, R. H. & BUKH, J. (2005) Cloning of a human parovirus by molecular screening of respiratory tract samples. *Proc Natl Acad Sci USA,* 102**,** 12891-6.

AMIEL-TISON, C. & STEWART, A. (1989) Follow up studies during the first five years of life: a pervasive assessment of neurological function. *Arch Dis Child,* 64**,** 496-502.

ASHER, M. I., KEIL, U., ANDERSON, H. R., BEASLEY, R., CRANE, J., MARTINEZ, F., MITCHELL, E. A., PEARCE, N., SIBBALD, B., STEWART, A. W. & ET, A. (1995) International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J,* 8**,** 483-491.

BAGLAJ, M., RUSSELL, G., SPICER, R. D., NOBLETT, H. R., MARLOW, N. & FLEMING, P. (1998) Congenital diaphragmatic hernia- 15 years experience with preoperative stabilisation. *Surg Childh Intern,* 6**,** 205-209.

BATES, J. H., ABE, T., ROMERO, P. V. & SATO, J. (1989a) Measurement of alveolar pressure in closed-chest dogs during interruption. *J Appl Physiol,* 67**,** 488-492.

BATES, J. H., BACONNIER, P. & MILIC-EMILI, J. (1988a) A theoretical analysis of interrupter technique for measuring respiratory mechanics. *J Appl Physiol,* 64**,** 2204-2214.

BATES, J. H., BROWN, K. A. & KOCHI, T. (1989b) Respiratory mechanics in the normal dog determined by expiratory flow interruption. *J Appl Physiol,* 67**,** 2276-2285.

BATES, J. H., LUDWIG, M. S., SLY, P. D., BROWN, K., MARTIN, J. G. & FREDBERG, J. J. (1988b) Interrupter resistance elucidated by alveolar pressure measurement in open-chest dogs. *J Appl Physiol,* 65**,** 408-414.

BATES, J. H. T., SLY, P. D., KOCHI, T. & MARTIN, J. G. (1987) The effect of a proximal compliance on interrupter measurements of resistance. *Respir Physiol,* 70**,** 301-312.

BEASLEY, J. M. & JONES, S. E. F. (1981) Continuous positive airway pressure in bronchiolitis. *Br Med J,* 283**,** 1506-1508.

BEELEN, R. M. J., SMIT, H. A., VAN STRIEN, R. T., KOOPMAN, L. P., BRUSSEE, J. E., BRUNEKREEF, B., GERRITSEN, J. & MERKUS, P. J. F. M. (2003) Short and long term variability of the interrupter technique under field and standardised conditions in 3-6 year old children. *Thorax,* 58**,** 761-764.

BEHRENDT, C. E., DECKER, M. D., BURCH, D. J. & WATSON, P. H. (1998) International variation in the management of infants hospitalised with respiratory syncytial virus. International RSV Study Group. *Eur J Pediatr,* 157**,** 215-220.

BISGAARD, H. & KLUG, B. (1995) Lung function measurements in awake young children. *Eur Respir J,* 8**,** 2067-2075.

BISGAARD, H. & STUDY GROUP ON MONTELUKAST AND RESPIRATORY SYNCYTIAL VIRUS (2003) A randomised trial of montelukast in respiratory syncytial virus postbronchiolitis. *Am J Respir Crit Care Med,* 167**,** 379-383.

BONT, L., HEIJNEN, C. J., KAVELAARS, A., AALDEREN, V. M. C., BRUS, F., DRAAISMA, J. M. T., GEELEN, S. M. & KIMPEN, J. L. L. (2000) Monocyte IL-10 production during respiratory syncytial virus bronchiolitis is associated with recurrent wheezing in a one-year follow-up study. *Am J Respir Crit Care Med,* 161**,** 1518-1523.

BONT, L., STEIJN, M., AALDEREN, V., BRUS, F., DRAAISMA, J., VAN DIEMEN-STEENVOORDE, R., PEKELHARING-BERGHUIS, M. & KIMPEN, J. (2004) Seasonality of long term wheezing following respiratory virus lower respiratory tract infection. *Thorax,* 59**,** 512-516.

BRAY, R. J. & MORRELL, P. (1982) A follow-up of the survivors of mechanical ventilation in a paediatric intensive care unit. *Intensive Care Med,* 8**,** 163-168.

BRIDGE, P., LEE, H. & SILVERMAN, M. (1996) A portable device based on the interrupter technique to measure bronchodilator response in school children. *Eur Respir J,* 9**,** 1368-1373.

BRIDGE, P. & MCKENZIE, S. (2000) Feasibility of spirometry and Rint in children 5-10 years for the measurement of bronchodilator responsiveness. *Arch Dis Child,* 82**,** G157.

BRIDGE, P. D. & MCKENZIE, S. A. (2001) Airway resistance measured by the interrupter technique: expiration or inspiration, mean or median? *Eur Respir J,* 17**,** 495-498.

CADE, A., BROWNLEE, K. G., CONWAY, S. P., HAIG, D., SHORT, A., BROWN, J., DASSU, D., MASON, S. A., PHILIPS, A., EGLIN, R., GRAHAM, M., CHETCUTI, A., CHATRATH, M., HUDSON, N., THOMAS, A. & CHETCUTI, P. A. J. (2000) Randomised placebo controlled trial of nebulised corticosteroids in respiratory syncytial viral bronchiolitis. *Arch Dis Child,* 82**,** 126-130.

CAHILL, J., MOORE, K. P. & WREN, W. S. (1983) Nasopharyngeal continuous positive airway pressure in the management of bronchiolitis. Ir Med J, 76, 191-2.

CAMBONIE, G., MILESI, C., FOURNIER-FAVRE, S., COUNIL, F., JABER, S., PICAUD, J. C. & MATECKI, S. (2006) Clinical effects of heliox administration for acute bronchiolitis in young infants. *Chest,* 129**,** 676-82.

CANE, R. S. & MCKENZIE, S. A. (2001) Parents' interpretations of children's respiratory symptoms on video. *Arch Dis Child,* 84**,** 31-34.

CANE, R. S., RANGANATHAN, R. S. & MCKENZIE, S. A. (2000) What do parents of wheezy children understand by "wheeze"? *Arch Dis Child,* 82**,** 327-332.

CARTER, E. R. (1997) It is time to consider standardizing the interrupter technique. *Eur Respir J,* 10**,** 1428-1429.

CARTER, E. R., STECENKO, A. A., POLLOCK, B. H. & JAEGER, M. J. (1994) Evaluation of the interrupter technique for the use of assessing airway obstruction in children. *Pediatr Pulmonol,* 17**,** 211-7.

CHAN, E. Y., BRIDGE, P. D., DUNDAS, I., PAO, C. S., HEALY, M. J. R. & MCKENZIE, S. A. (2003) Repeatability of airway resistance measurements made using the interrupter technique. *Thorax,* 58**,** 344-347.

CHENG, K., ZHANG, H., LIN, C. & SLUTSKY, A. S. (2002) Ventilation with negative airway pressure induces a cytokine response in isolated mouse lung. *Anesth Analg,* 94**,** 1577-1582.

CHERNICK, V. & VIDYASAGAR, D. (1972) Continuous negative chest wall pressure in hyaline membrane disease: one year experience. *Pediatrics,* 49**,** 753-760.

CHOWIENCZYK, P., LAWSON, C., LANE, S., JOHNSON, R., WILSON, N., SILVERMAN, M. & COCHRANE, G. (1991) A flow interruption device for measurement of airway resistance. *Eur Respir J,* 4**,** 623-628.

CORCORAN, J. D., LEE, S. K., WHYTE, R., THIESSEN, P. & THE CANADIAN NICU NETWORK (1998) Neonatal Acute Physiology Parameters Index (NAPPI) - an efficient illness severity score for neonates. *Pediatr Res,* 44**,** 424.

CORNELI, H. M., ZORC, J. J., MAHAJAN, P., SHAW, K. N., HOLUBKOV, R., REEVES, S. D., RUDDY, R. M., MALIK, B., NELSON, K. A., BREGSTEIN, J. S., BROWN, K. M., DENENBERG, M. N., LILLIS, K. A., CIMPELLO, L. B., TSUNG, J. W., BORGIALLI, D. O., BASKIN, M. N., TESHOME, G., GOLDSTEIN, M. A., MONROE, D., DEAN, M., KUPPERMANN, N. & FOR THE BRONCHIOLITIS STUDY GROUP OF THE PEDIATRIC EMERGENCY CARE APPLIED RESEARCH NETWORK (PECARN) (2007) A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. *N Engl J Med,* 357**,** 331-339.

CORRADO, A., GORINI, M., VILLELLA, G. & DE PAOLA, E. (1996) Negative pressure ventilation in the treatment of acute respiratory failure: an old noninvasive technique reconsidered. *Eur Respir J.,* 9**,** 1531-44.

CVETNIC, W. G., CUNNINGHAM, M. D., SILLS, J. H. & GLUCK, L. (1990) Reintroduction of continuous negative pressure ventilation in neonates: two-year experience. *Pediatr Pulmonol.,* 8**,** 245-53.

CVETNIC, W. G., SHOPTAUGH, M. & SILLS, J. H. (1992) Intermittent mandatory ventilation with continuous negative pressure compared with positive end-expiratory pressure for neonatal hypoxaemia. *J Perinat,* 12**,** 316-324.

DOBSON, J. V., STEPHENS-GROFF, S. M., MCMAHON, S. R., STEMMLER, M. M., BRALLIER, S. L. & BAY, C. (1998) The Use of Albuterol in Hospitalized Infants With Bronchiolitis. *Pediatrics,* 101**,** 361-368.

DOWNES, J. J. & STRIKER, T. W. (1966) Acute respiratory failure in infants and children with bronchiolitis, pneumonitis and status asthmaticus. *Acta Anaesthesiol Suppl,* 23**,** 747 -757.

DRINKER, P. & SHAW, L. A. (1929) An apparatus for the prolonged administration of artificial respiration. I. A design for adults and children. *J Clin Invest,* 7**,** 229-247.

DUNDAS, I. & MCKENZIE, S. (2003) Measurement of lung function in preschool children. *The Airways Journal,* 1**,** 30-33.

DUVAL, E. L. I. M., LEROY, P. L. J. M., GEMKE, R. J. B. J. & VAN VUGHT, A. J. (1999) High-frequency oscillatory ventilation in RSV bronchiolitis patients. *Respir Med,* 93**,** 435-440.

EDELL, D., KHOSHOO, V., ROSS, G. & SALTER, K. (2002) Early ribavirin treatment of bronchiolitis: Effect on long-term respiratory morbidity. *Chest,* 122**,** 935-939.

EDWARDS, P., ROBERTS, I., CLARKE, M., DIGUISEPPI, C., PRATAP, S., WENTZ, R. & KWAN, I. (2002) Increasing response rates to postal questionnaires: systematic review. *Br Med J,* 324**,** 1183-.

EISEN, A. H. & BACAL, H. L. (1963) The relationship of acute bronchiolitis to bronchial asthma - a 4 to 14 year follow up. *Pediatrics,* 31**,** 859-861.

ELPHICK, H. E., RITSON, S., RIGBY, A. S. & EVERARD, M. L. (2007) Phenotype of acute respiratory syncytial virus induced lower respiratory tract illness in infancy and subsequent morbidity. *Acta Paediatr,* 96**,** 307-9.

ESSA, D., MUNDIE, T. G., FINN, K. C., HASHIRO, G. & BALARAMAN, V. (1994) Continuous negative extrathoracic pressure versus positive end-expiratory pressure in piglets after saline lung lavage. *Pediatr Pulmonol,* 17**,** 161-168.

ESSOURI, S., CHEVRET, L., DURAND, P., HAAS, V., FAUROUX, B. & DEVICTOR, D. (2006) Noninvasive positive pressure ventilation: five years of experience in a pediatric intensive care unit. *Pediatr Crit Care Med,* 7**,** 329-34.

EVERARD, M. L. (2006a) The relationship between respiratory syncytial virus infections and the development of wheezing and asthma in children. *Curr Opin Allergy Clin Immunol,* 6**,** 56-61.

EVERARD, M. L. (2006b) The role of the respiratory syncytial virus in airway syndromes in childhood. *Curr Allergy Asthma Rep,* 6**,** 97-102.

FANAROFF, A., CHOON CHA, C., SOSA, R., CRUMRINE, R. & KLAUS, M. (1973) Controlled trial of continuous negative external pressure in the treatment of severe respiratory distress syndrome. *J Pediatr,* 82**,** 921-928.

FEENY, D. H., TORRANCE, G. W. & FURLONG, W. J. (1996) Health Utilities Index. IN SPIKER, B. (Ed.) *Quality of life and pharmacoeconomics in clinical trials.* Second ed. Philadelphia, Lippincott-Raven Publishers.

FELTES, T. F., CABALKA, A. K., MEISSNER, H. C., PIAZZA, F. M., CARLIN, D. A., TOP, F. H., CONNOR, E. M. & SONDHEIMER, H. M. (2003) Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant heart disease. *J Pediatr,* 143**,** 532-40.

FLAMANT, C., HALLALEL, F., NOLENT, P., CHEVALIER, J. Y. & RENOLLEAU, S. (2005) Severe respiratory syncytial virus bronchiolitis in children: from short mechanical ventilation to extracorporeal membrane oxygenation. *Eur J Pediatr,* 164**,** 93-8.

FOULONGNE, V. P., GUYON, G. M. D., RODIERE, M. M. D. & SEGONDY, M. P. (2006) Human Metapneumovirus Infection in Young Children Hospitalized With Respiratory Tract Disease. *Pediatr. Infect. Dis. J,* 25**,** 354-359.

FOWLIE, P. W., GOULD, C. R., TARNOW-MORDI, W. O. & STRANG, D. (1998) Measurement properties of the Clinical Risk Index for Babies-reliability, validity beyond the first 12 hours and responsiveness over 7 days. *Crit Care Med,* 26**,** 163-168.

FOX, G. F., EVERARD, M. I., MARSH, M. J. & MILNER, A. D. (1999) Randomized controlled trial of budesonide for the prevention of post bronchiolitis wheezing. *Arch Dis Child,* 80**,** 343-347.

GAPPA, M., COSTELOE, K., SOUTHALL, D. P., RABBETTE, P. S. & STOCKS, J. (1994) Effect of continuous negative extrathoracic pressure on respiratory mechanics and timing in infants recovering from neonatal respiratory distress syndrome. *Pediatr Res,* 36**,** 364-72.

GARDNER, P. S. (1968) Virus infections and respiratory disease of childhood. *Arch Dis Child,* 43**,** 629-645.
GOODMAN, R. (1997) The Strengths and Difficulties Questionnaire: a research note. *J Child Psychol Psychiatry,* 38**,** 581-6.
GOODMAN, R. (1999) The extended version of the Strengths and Difficulties Questionnaire as a guide to child psychiatric caseness and consequent burden. *J Child Psychol Psychiatry,* 40**,** 791-9.
GOODMAN, R. (2001) Psychometric properties of the strengths and difficulties questionnaire. *J Am Acad Child Adolesc Psychiatry,* 40**,** 1337-45.
GOODMAN, R., FORD, T., SIMMONS, H., GATWARD, R. & MELTZER, H. (2000) Using the Strengths and Difficulties Questionnaire (SDQ) to screen for child psychiatric disorders in a community sample. *Br J Psychiatry,* 177**,** 534-539.
GOODMAN, R., MELTZER, H. & BAILEY, V. (1998) The Strengths and Difficulties Questionnaire: a pilot study on the validity of the self-report version. *Eur Child Adolesc Psychiatry,* 7**,** 125-30.
GREENOUGH, A., ALEXANDER, J., BURGESS, S., BYTHAM, J., CHETCUTI, P. A. J., HAGAN, J., LENNEY, W., MELVILLE, S., SHAW, N. J., BOORMAN, J., COLES, S., TURNER, J. & PANG, F. (2004) Health care utilisation of prematurely born, preschool children related to hospitalisation for RSV infection. *Arch Dis Child,* 89**,** 673-678.
GRIFFITHS (2003) Report of a review of the research framework in North Staffordshire Hospital NHS Trust. *http://www.dh.gov.uk/assetRoot/04/01/45/42/04014542.pdf*.
GROOTHUIS, J. R., SIMOES, E., LEVIN, M. J., HALL, C. B., LONG, C. E., RODRIGUEZ, W. J., ARROBIO, J., MEISSNER, H. C., FULTON, D. R., WELLIVER, R. C., TRISTRAM, D. A., SIBER, G. R., PRINCE, G. A., VAN RADEN, M., HEMMING, V. G. & THE RESPIRATORY SYNCYTIAL VIRUS IMMUNE GLOBULIN STUDY GROUP (1993) Prophylactic Administration of Respiratory Syncytial Virus Immune Globulin to High-Risk Infants and Young Children. *N Engl J Med,* 329**,** 1524-1530.
GROOTHUIS, J. R., WOODIN, K. A., KATZ, R., ROBERTSON, A. D., MCBRIDE, J. T., HALL, C. B., MCWILLIAMS, B. C. & LAUER, B. A. (1990) Early ribavirin treatment of respiratory syncytial viral infection in high-risk children. *J Pediatr,* 117**,** 792-8.
GURWITZ, D., MINDORFF, C. & LEVISON, H. (1981) Increased incidence of bronchial reactivity in children with a history of bronchiolitis. *J Pediatr,* 98**,** 551-55.
HALL, C., GEIMAN, J., BIGGAR, R., KOTOK, D., HOGAN, P. & DOUGLAS, R. J. (1976) Respiratory syncytial virus infection within families. *N Engl J Med,* 294**,** 414 - 419.
HALL, C. B. (1998) Respiratory syncytial virus. IN FEIGIN, R. D. & CHERRY, J. D. (Eds.) *Textbook of pediatric Infectious Diseases.* Philadelphia, W B Saunders.
HALL, C. B., HALL, W. J., GALA, C. L., MAGILL, F. B. & LEDDY, J. P. (1984) Long-term prospective study in children after respiratory syncytial virus infection. *J Pediatr,* 105**,** 358-364.
HAMMER, J. & EBER, E. (Eds.) (2005) *Paediatric pulmonary function testing,* Basel, Karger.
HANDFORTH, J., FRIEDLAND, J. S. & SHARLAND, M. (2000) Basic epidemiology and immunopathy of RSV in children. *Paediatr Respir Rev,* 1**,** 210-214.

HARTMANN, H., JAWAD, M. H., NOYES, J., SAMUELS, M. P. & SOUTHALL, D. P. (1994a) Negative extrathoracic pressure ventilation in central hypoventilation syndrome. *Arch Dis Child.,* 70**,** 418-23.

HARTMANN, H., NOYES, J. P., WRIGHT, T., WHEATLEY, R., SPENCER, A., BOON, A., ALEXANDER, J., SAMUELS, M. P. & SOUTHALL, D. P. (1994b) Continuous negative extrathoracic pressure ventilation in infants with bronchiolitis. *Eur Respir J,* 7**,** 379s.

HENRY, R. L., HODGES, I. G. C., MILNER, A. D. & STOKES, G. M. (1983) Respiratory problems 2 years after acute bronchiolitis in infancy. *Arch Dis Child,* 58**,** 713-716.

HO, L., COLLIS, G., LANDAU, L. & LE SOUEF, P. (1991) Effect of salbutamol on oxygen saturation in bronchiolitis. *Arch Dis Child,* 66**,** 1061-1064.

HODGE, D. & CHETCUTI, P. A. J. (2000) RSV: Management of the acute episode. *Paediatr Respir Rev,* 1**,** 215-220.

HOLLMAN, G., SHEN, G. & ZENG, L. (1998) Helium-oxygen improves clinical asthma scores in children with acute bronchiolitis. *Crit Care Med,* 26**,** 1731-1736.

JARTTI, T., MAKELA, M. J., VANTO, T. & RUUSKANEN, O. (2005) The link between bronchiolitis and Asthma. *Infect Dis Clin North Am,* 19**,** 667 - 689.

JENKINS, M. A., CLARKE, J. R., CARLIN, J. B., ROBERTSON, C. F., HOPPER, J. L., DALTON, M. F., HOLST, D. P., CHOI, K. & GILES, G. G. (1996) Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int. J. Epidemiol.,* 25**,** 609-616.

JOINT COMMITTEE ON VACCINATION AND IMMUNISATION (2005) Minutes of the meeting held on Wednesday 22nd June 2005. http://www.advisorybodies.doh.gov.uk/jcvi/mins220605.htm.

KAJOSAARI, M., SYVANEN, P., FORARS, M. & JUNTUNEN-BACKMAN, K. (2000) Inhaled corticosteroids during and after respiratory syncytial virus-bronchiolitis may decrease subsequent asthma. *Pediatr Allergy Immunol,* 11**,** 198-202.

KAPIKIAN, A. Z., MITCHELL, R. H., CHANOCK, R. M., SHVEDOFF, R. A. & STEWART, C. E. (1969) An epidemiologic study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RS vaccine. *Am J Epidemiol,* 89**,** 405-421.

KELLNER, J. D., OHLSSON, A., GADOMSKI, A. M. & WANG, E. E. (2000) Bronchodilators for bronchiolitis. *Cochrane Database of Sys Rev***,** CD001266.

KIM, H. W., CANCHOLA, J. G., BRANDT, C. D., PYLES, G., CHANOCK, R. M., JENSEN, K. & PARROTT, R. H. (1969) Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. *Am J Epidemiol,* 89**,** 422-434.

KIMPEN, J. L. L. (2002) Prevention and treatment of respiratory syncytial virus bronchiolitis and post bronchiolitis wheezing. *Respir Res,* 3**,** S40-S45.

KLASSEN, T. P., ROWE, P. C., SUTCLIFFE, T., ROPP, L. J., MCDOWELL, I. W. & LI, M. M. (1991) Randomized trial of salbutamol in acute bronchiolitis. *J Pediatr,* 118**,** 807-11.

KLONIN, H., CAMPBELL, C., HAWTHORN, J., SOUTHALL, D. P. & SAMUELS, M. P. (2000) Negative extrathoracic pressure in infants with cystic fibrosis and respiratory failure. *Pediatr Pulmonol,* 30**,** 260-264.

KLUG, B. & BISGAARD, H. (1998) Specific airway resistance, interrupter resistance and respiratory impedance in healthy children aged 2-7 years. *Pediatr Pulmonol,* 25**,** 322-331.
KNEYBER, M., MOLL, H. & DE GROOT, R. (2000) Treatment and prevention of respiratory syncytial virus infection. *Eur J Pediatr,* 159**,** 399 - 411.
KOOI, E. M. W., VRIJLANDT, E. J. L. E., MARIKE BOEZEN, H. & DUIVERMAN, E. J. (2004) Children with smoking parents have a higher airway resistance measured by the interruption technique. *Pediatr Pulmonol,* 38**,** 419-424.
KORHONEN, P., LAITINEN, J., HYODYNMAA, E. & TAMMELA, O. (2004) Respiratory outcome in school-aged, very-low-birth-weight children in the surfactant era. *Acta Paediatrica,* 93**,** 316-21.
KORPPI, M., REIJONEN, T., POYSA, L. & JUNTUNEN-BACKMAN, K. (1993) A 2 to 3 year outcome after bronchiolitis. *Am J Dis Child,* 147**,** 628 - 631.
KOTANIEMI-SYRJANEN, A., VAIIONPAA, R., REIJONEN, T. M., WARIS, M., KORHONEN, K. & KORPPI, M. (2003) Rhinovirus-induced wheezing in infancy--the first sign of childhood asthma? *J Allergy Clin Immunol,* 111**,** 66 -71.
KRAEMER, S. (2000) The fragile male. *Br Med J,* 321**,** 1609-1612.
LASSEN, H. (1953) A preliminary report on the 1952 epidemic of poliomyelitis in Copenhagen with special reference to the treatment of acute respiratory insufficiency. *Lancet,* 261**,** 37-41.
LAW, B. J., WANG, E. E. L., MACDONALD, N., MCDONALD, J., DOBSON, S., BOUCHER, F., LANGLEY, J., ROBINSON, J., MITCHELL, I. & STEPHENS, D. (1997) Does Ribavirin Impact on the Hospital Course of Children With Respiratory Syncytial Virus (RSV) Infection? An Analysis Using the Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) RSV Database. *Pediatrics,* 99**,** e7-.
LEBEL, M. H., GAUTHIER, M., LACROIX, J., ROUSSEAU, E. & BUITHIEU, M. (1989) Respiratory failure and mechanical ventilation in severe bronchiolitis. *Arch Dis Child,* 64**,** 1431-7.
LECLERC, F., SCALFARO, P., NOIZET, O., THUMERELLE, C., DORKENOO, A. & FOURIER, C. (2001) Mechanical ventilatory support in infants with respiratory syncytial virus infection. *Pediatr Crit Care Med, 2***,** 197-204.
LIET, J. M., MILLOTTE, B., TUCCI, M., LAFLAMMME, S., HUTCHISON, J., CREERY, D., DUCRUET, T., LACROIX, J. & CANADIAN CRITICAL CARE TRIALS, G. (2005) Noninvasive therapy with helium-oxygen for severe bronchiolitis. *J Pediatr,* 147**,** 812-7.
LINNEY, M. J., MARINAKI, T., SOUTHALL, D. P. & SAMUELS, M. P. (1997) Negative pressure ventilation in bronchiolitis. *Care of the Critically Ill.,* 13**,** 161.
LOMBARDI, E., SLY, P. D., CONCUTELLI, G., NOVEMBRE, E., VENERUSO, G., FRONGIA, G., BERNARDINI, R. & VIERUCCI, A. (2001) Reference values of interrupter respiratory resistance in healthy preschool white children. *Thorax,* 56**,** 691-695.
LONG, C. E., VOTER, K. Z., BARKER, W. H. & HALL, C. B. (1997) Long-term follow-up of children hospitalized with respiratory syncytial virus lower respiratory tract infection and randomly treated with ribavarin or placebo. *Pediatr Infect Dis,* 16**,** 1023-1028.

MARLOW, N., WOLKE, D., BRACEWELL, M. A., SAMARA, M. & THE EPICURE STUDY GROUP (2005) Neurologic and developmental disability at six years of age after extremely preterm birth. *N Engl J Med,* 352**,** 9-19.

MARTINEZ, F., MORGAN, W., WRIGHT, A., HOLBERG, C. & TAUSSIG, L. (1988) Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N Engl J Med,* 319**,** 1112-1117.

MCCONNOCHIE, K. M. & ROGHMANN, K. J. (1984) Bronchiolitis as a possible cause of wheezing in childhood: New evidence. *Pediatrics,* 74**,** 1-10.

MCCONNOCHIE, K. M. & ROGHMANN, K. J. (1989) Wheezing at 8 and 13 years: Changing importance of bronchiolitis and passive smoking. *Pediatr Pulmonol,* 6**,** 138-146.

MCKENZIE, S., BRIDGE, P. & HEALY, M. (2000) Airway resistance and atopy in preschool children with wheeze and cough. *Eur Respir J,* 15**,** 833-838.

MCKENZIE, S. A., CHAN, E., DUNDAS, I., BRIDGE, P. D., PAO, C. S., MYLONOPOULOU, M. & HEALY, M. J. R. (2002) Airway resistance measured by the interrupter technique: normative data for 2-10 year olds of three ethnicities. *Arch Dis Child,* 87**,** 248-251.

MELLINS, R. B., CHERNICK, V., DOERSHUK, C. F., DOWNES, J. J., SINCLAIR, J. C. & WARING, W. W. (1972) Respiratory care in infants and children. *Am Rev Respir Dis*, 105**,** 461 - 483.

MERKUS, P. J. F. M., ARETS, H. G. M., JOOSTEN, T., SIERO, A., BROUHA, M., MIJNSBERGEN, J. Y., DE JONGSTE, J. C. & VAN DER ENT, C. K. (2002) Measurements of interrupter resistance: reference values for children 3-13 yrs of age. *Eur Respir J,* 20**,** 907-911.

MERKUS, P. J. F. M., MIJNSBERGEN, J. Y., HOP, W. C. J. & DE JONGSTE, J. C. (2001) Interrupter Resistance in Preschool Children. Measurement Characteristics and Reference Values. *Am. J. Respir. Crit. Care Med.,* 163**,** 1350-1355.

MILLER, M., HANKINSON, J., BRUSASCO, V., BURGOS, F., CASABURI, R., COATES, A., CRAPO, R., ENRIGHT, P., VAN DER GRINTEN, C., GUSTAFSSON, P., JENSEN, R., JOHNSON, D., MACINTYRE, N., MCKAY, R., NAVAJAS, D., PEDERSEN, O., PELLEGRINO, R., VIEGI, G. & WANGER, J. (2005) Standardisation of spirometry. *Eur Respir J,* 26**,** 319-338.

MOK, J. Y. Q. & SIMPSON, H. (1984) Outcome for acute bronchitis, bronchiolitis and pneumonia in infancy. *Arch Dis Child,* 59**,** 306-309.

MONIN, P., CASHMORE, W., HAKANSON, D., COWETT, R. & OH, W. (1976) Assisted ventilation in the neonate - Comparison between positive and negative ventilators. *Pediatr Res,* 10**,** 464.

MURRAY, M., WEBB, M. S. C., O'CALLAGHAN, C., SWARBRICK, A. S. & MILNER, A. D. (1992) Respiratory status and allergy after bronchiolitis. *Arch Dis Child,* 67**,** 482-487.

NATIONAL PERINATAL EPIDEMIOLOGY UNIT AND OXFORD HEALTH AUTHORITY (1995) Report of two working groups. Disability and perinatal care: Measurement of health status at two years.

NAVAS, L., WANG, E., DE CARVALHO, V. & ROBINSON, J. (1992) Improved outcome of respiratory syncytial virus infection in a high-risk hospitalized population of Canadian children. Pediatric Investigators Collaborative Network on Infections in Canada. *J Pediatr,*121**,** 348-54.

NIELSEN, K. G. & BISGAARD, H. (2000) The effect of inhaled budesonide on symptoms, lung function, and cold air and methacholine responsiveness in 2- to 5-year-old asthmatic children. *Am J Respir Crit Care Med,* 162**,** 1500-6.

NOBLE, V., MURRAY, M., WEBB, M. S. C., ALEXANDER, J., SWARBRICK, A. S. & MILNER, A. D. (1997) Respiratory status and allergy nine to 10 years after bronchiolitis. *Arch Dis Child,* 76**,** 315-319.

ORLOWSKI, J. P., ELLIS, N. G., AMIN, N. P., CRUMRINE, R. S. & SMITH, R. M. (1980) Complications of Airway Intrusion in 100 Consecutive Cases in a Pediatric ICU. *Crit Care Med,* 8**,** 324-331.

OSUNDWA, V. M. (1993) Recurrent wheezing in children with respiratory syncytial virus (RSV) bronchiolitis in Qatar. *Eur J Pediatr,* 152**,** 1001-1003.

OSWALD-MAMMOSSER, M., CHARLOUX, A., DONATO, L., ALBRECH, C., SPEICH, J. P., LAMPERT, E. & LONSDORFER, J. (2000) Interrupter technique versus plethysmography for measurement of respiratory resistance in children with asthma or cystic fibrosis. *Pediatr Pulmonol,* 29**,** 213-220.

OSWALD-MAMMOSSER, M., LLERENA, C., SPEICH, J. P., DONATA, L. & LONSDORFER (1997) Measurements of respiratory system resistance by the interrupter technique in healthy and asthmatic children. *Pediatr Pulmonol,* 24**,** 78-85.

OUTERBRIDGE, E., ROLOFF, D. & STERN, L. (1972) Continuous negative pressure in the management of severe respiratory distress syndrome. *J Pediatr,* 81**,** 384-391.

OUTWATER, K. M. & CRONE, R. K. (1984) Management of respiratory failure in infants with acute viral bronchiolitis. *Am J Dis Child,* 138**,** 1071-1075.

PALISANO, R., ROSENBAUM, P., WALTER, S., RUSSELL, D., WOOD, E. & GALUPPI, B. (1997) Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol,* 39**,** 214-223.

PALMER, K., SPENCER, S. A., WICKRAMASINGHE, Y., WRIGHT, T., SAMUELS, M. & ROLFE, P. (1994) Negative extrathoracic pressure ventilation--evaluation of the neck seal. *Early Hum Dev,* 37**,** 67-72.

PALMER, K. S., SPENCER, S. A., WICKRAMASINGHE, Y. A., WRIGHT, T., SOUTHALL, D. P. & ROLFE, P. (1995) Effects of positive and negative pressure ventilation on cerebral blood volume of newborn infants. *Acta Paediatrica.,* 84**,** 132-9.

PAO, C. S., HEALY, M. J. R. & MCKENZIE, S. A. (2004) Airway resistance by the interrupter technique: Which algorithm for measuring pressure? *Pediatr Pulmonol,* 37**,** 31-36.

PAO, C. S. & MCKENZIE, S. A. (2002) Randomised controlled trial of fluticasone in preschool children with intermittent wheeze. *Am J Respir Crit Care Med,* 166**,** 945-949.

PATEL, H., PLATT, R., LOZANO, J. M. & WANG, E. E. (2004) Glucocorticoids for acute viral bronchiolitis in infants and young children. *Cochrane Database of Systematic Reviews***,** CD004878.

PHAGOO, S. B., WILSON, N. M. & SILVERMAN, M. (1995) Evaluation of the interrupter technique for measuring change in airway resistance in 5-year-old asthmatic children. *Pediatr Pulmonol,* 20**,** 387-395.

PHAGOO, S. B., WILSON, N. M. & SILVERMAN, M. (1996) Evaluation of a new interrupter device for measuring bronchial responsiveness and the response to bronchodilator in 3 year old children. *Eur Respir J,* 9**,** 1374-1380.

PICANET NATIONAL REPORT (2006) National Report of the Paediatric Intensive Care Audit Network. http://www.picanet.leeds.ac.uk/Documents/General/National%20report%202006_amended_1.pdf.

PIEDIMONTE, G. (2001) Neural mechanisms of respiratory syncytial virus-induced inflammation and prevention of respiratory syncytial virus sequelae. *Am J Respir Crit Care Med,* 163**,** S18- S21.

PIEDIMONTE, G., KING, K. A., HOLMGREN, N. L., BERTRAND, P. J., RODRIGUEZ, M. M. & HIRSCH, R. L. (2000) A humanised monoclonal antibody against respiratory syncytial virus (Palivizumab) inhibits RSV-induced neurogenic-mediated inflammation in rat airways. *Pediatr Res,* 47**,** 351-356.

PIEDIMONTE, G., RENZETTI, G., AUAIS, A., DI MARCO, A., TRIPODI, S., COLISTRO, F., VILLANI, A., DI CIOMMO, V. & CUTRERA, R. (2005) Leukotriene synthesis during respiratory syncytial virus bronchiolitis: influence of age and atopy. *Pediatr Pulmonol,* 40**,** 285-91.

PIEDIMONTE, G., RODRIGUEZ, M., KING, K., MCLEAN, S. & JIANG, X. (1999) Respiratory syncytial virus upregulates expression of the substance P receptor in rat lungs. *Am J Physiol,* 277**,** L831-840.

POLLACK, M. M., PATEL, K. M. & RUTTIMANN, U. E. (1996) PRISM III: An updated Pediatric Risk of Mortality score. *Crit Care Med,* 24**,** 743-752.

POLLACK, M. M., RUTTIMANN, U. E. & GETSON, P. R. (1987) Accurate prediction of the outcome of pediatric intensive care. A new quantitative method. *N Engl J Med,* 316**,** 134-139.

PRIFTIS, K., EVERARD, M. & MILNER, A. D. (1990) Outcome of severe acute bronchiolitis needing mechanical ventilation. *The Lancet,* 335**,** 607.

PULLAN, C. R. & HEY, E. N. (1982) Wheezing, asthma and pulmonary dysfunction 10 years after infection with respiratory syncytial virus infection in infancy. *Br Med J,* 284**,** 1665-1669.

RAINE, J., COWAN, F., SAMUELS, M. P., WERTHEIM, D. & SOUTHALL, D. P. (1994) Continuous negative extrathoracic pressure and cerebral blood flow velocity: a pilot study. *Acta Paediatrica.,* 83**,** 438-9.

RAINE, J., SAMUELS, M. P., MOK, Q., SHINEBOURNE, E. A. & SOUTHALL, D. P. (1992) Negative extrathoracic pressure ventilation for phrenic nerve palsy after paediatric cardiac surgery. *Br Heart J,* 67**,** 308-311.

RAMESH, P. & SAMUELS, M. (2005) Are methylxanthines effective in preventing or reducing apnoeic spells in infants with bronchiolitis? *Arch Dis Child,* 90**,** 321-322.

RANDALL CURTIS, J. (2002) The long-term outcomes of mechanical ventilation: what are they and how should they be used? *Respir Care,* 47**,** 496-505.

RANDOLPH, A. G., MEERT, K. L., O'NEIL, M. E., HANSON, J. H., LUCKETT, P. M., ARNOLD, J. H., GEDEIT, R. G., COX, P. N., ROBERTS, J. S., VENKATARAMAN, S. T., FORBES, P. W. & CHEIFETZ, I. M. (2003) The Feasibility of Conducting Clinical Trials in Infants and Children with Acute Respiratory Failure. *Am. J. Respir. Crit. Care Med.,* 167**,** 1334-1340.

RANIERI, V. M., SUTER, P. M., TORTORELLA, C., DE TULLIO, R., DAYER, J. M., BRIENZA, A., BRUNO, F. & SLUTSKY, A. S. (1999) Effect of Mechanical Ventilation on Inflammatory Mediators in Patients With Acute Respiratory Distress Syndrome: A Randomized Controlled Trial. *JAMA,* 282**,** 54-61.

REIJONEN, T., KORPPI, M., KUIKKA, L. & REMES, K. (1996) Anti-inflammatory therapy reduces wheezing after bronchiolitis. *Arch Pediatr Adolesc Med,* 150**,** 512-517.
RENZI, P. M., TURGEON, J. P., YANG, J. P., DRBLIK, S. P., MARCOTTE, J. E., PEDNEAULT, L. & SPIER, S. (1997) Cellular immunity is activated and a TH-2 response is associated with early wheezing in infants after bronchiolitis. *J Pediatr,* 130**,** 584-593.
RICHARDSON, D. K., CORCORAN, J. D., ESCOBAR, G. J. & LEE, S. K. (2001) SNAP-II and SNAPPE-II: Simplified newborn illness severity and mortality risk scores. *J Pediatr,* 138**,** 92-100.
RIORDAN, F. A., MARZOUK, O., THOMSON, A. P., SILLS, J. A. & HART, C. A. (2002) Prospective validation of the Glasgow Meningococcal Septicaemia Prognostic Score. Comparison with other scoring methods. *Eur J Pediatr,* 161**,** 531-7.
RODRIGUEZ, W. J., ARROBIO, J., FINK, R., KIM, H. W. & MILBURN, C. (1999) Prospective follow-up and pulmonary functions from a placebo-controlled randomised trial of ribavirin therapy in Respiratory Syncytial Virus bronchiolitis. *Arch Pediatr Adolesc Med,* 153**,** 469-474.
ROGERS, A., MURTAUGH, M. A., EDWARDS, S. & SLATTERY, M. L. (2004) Contacting Controls: Are We Working Harder for Similar Response Rates, and Does It Make a Difference? *Am. J. Epidemiol.,* 160**,** 85-90.
ROTHMAN, K. J. & GREENLAND, S. (1998) *Modern Epidemiology, pg 284,* Philadelphia, PA, Lippincott-Raven.
ROUSSOS, C. & KOUTSOUKOU, A. (2003) Respiratory failure. *Eur Respir J,* 22**,** 3S-14.
ROYAL CHILDREN'S HOSPITAL WEBSITE The use of aminophylline in infants with bronchiolitis. http://www.rch.org.au/neonatal_rch/research.cfm?doc_id=6944 Last accessed 21st Feb 2008, Last updated 11th Dec 2006.
RYLANDER, E., ERIKSSON, M. & FREYSCHUSS, U. (1988) Risk factors for occasional and recurrent wheezing after RSV infection in infancy. *Acta Paediatrica Scandinavica,* 77**,** 711-5.
SAIGAL, S., ROSENBAUM, P., STOSKOPF, B., HOULT, L., FURLONG, W., FEENY, D., BURROWS, E. & TORRANCE, G. (1994) Comprehensive assessment of the health status of extremely low birth weight children at eight years of age: comparison with a reference group. *J Pediatr,* 125**,** 411-7.
SAMUELS, M. & BOIT, P. (2007) Non-invasive ventilation in children. *Paediatr Child Health,* 17**,** 167-173.
SAMUELS, M. P., RAINE, J., WRIGHT, T., ALEXANDER, J. A., LOCKYER, K., SPENCER, S. A., BROOKFIELD, D. S., MODI, N., HARVEY, D., BOSE, C. & SOUTHALL, D. P. (1996) Continuous negative extrathoracic pressure in neonatal respiratory failure. *Pediatrics.,* 98**,** 1154-60.
SAMUELS, M. P. & SOUTHALL, D. P. (1989) Negative extrathoracic pressure in treatment of respiratory failure in infants and young children. *Br Med J,* 299**,** 1253-7.
SCHUH, S., CANNY, G., REISMAN, J., KEREM, E., BENTUR, L., PETRIC, M. & LEVISON, H. (1990) Nebulised albuterol in acute bronchiolitis. *J Pediatr.,* 117**,** 633-637.
SHAY, D. K., HOLMAN, R. C., NEWMAN, R. D., LIU, L. L., STOUT, J. W. & ANDERSON, L. J. (1999) Bronchiolitis-associated hospitalizations among US children, 1980-1996. *JAMA.,* 282**,** 1440-6.

SHEKERDEMIAN, L. S., BUSH, A., SHORE, D. F., LINCOLN, C. & REDINGTON, A. N. (1997) Cardiopulmonary interactions after Fontan operations: augmentation of cardiac output using negative pressure ventilation. *Circulation,* 96**,** 3934-42.

SHEKERDEMIAN, L. S., BUSH, A., SHORE, D. F., LINCOLN, C. & REDINGTON, A. N. (1999) Cardiorespiratory responses to negative pressure ventilation after tetralogy of Fallot repair: a hemodynamic tool for patients with a low-output state. *J Am Coll Cardiol,* 33**,** 549.

SIGURS, N., BJARNASON, R., SIGURBERGSSON, F. & KJELLMAN, B. (2000) Respiratory Syncytial Virus Bronchiolitis in Infancy Is an Important Risk Factor for Asthma and Allergy at Age 7. *Am. J. Respir. Crit. Care Med.,* 161**,** 1501-1507.

SIGURS, N., BJARNASON, R., SIGURSBERGSSON, F., KJELLMAN, B. & BRORKSTEN, B. (1995) Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: a prospective cohort study with matched controls. *Pediatrics,* 95**,** 500-505.

SIMS, D. G., DOWNHAM, M. A. P. S., GARDNER, P. S., WEBB, J. K. G. & WEIGHTMAN, D. (1978) Study of 8 year old children with a history of respiratory syncytial virus bronchiolitis in infancy. *Br Med J,* 1**,** 11-14.

SLUTSKY, A. S. (1999) Lung injury caused by mechanical ventilation. *Chest,* 116**,** 9S-15S.

SLY, P. D. & HIBBERT, M. E. (1989) Childhood asthma following hospitalisation with acute viral bronchiolitis in infancy. *Pediatr Pulmonol,* 7**,** 153-158.

SLY, P. D. & LOMBARDI, E. (2003) Measurement of lung function in preschool children using the interrupter technique. *Thorax,* 58**,** 742-744.

SOONG, W. J., HWANG, B. & TANG, R. B. (1993) Continuous positive airway pressure by nasal prongs in bronchiolitis. *Pediatr pulmonol,* 16**,** 163-6.

SPORIK, R. (1994) Why block a small hole? The adverse effects of nasogastric tubes. *Arch Dis Child,* 71**,** 393-394.

STADE, B. C., STEVENS, B., UNGAR, W. J., BEYENE, J. & KOREN, G. (2006) Health-related quality of life of Canadian children and youth prenatally exposed to alcohol. *Health Qual Life Outcomes,* 4**,** 81.

STEIN, R. T., SHERRILL, D., MORGAN, W. J., HOLBERG, C. J., HALONEN, M., TAUSSIG, L. M., WRIGHT, A. L. & MARTINEZ, F. D. (1999) Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet.,* 354**,** 541-5.

STELMACH, I., GRZELEWSKI, T., BOBROWSKA-KORZENIOWSKA, M., STELMACH, P., KUNA, P. (2007) A randomized, double-blind trial of the effect of anti-asthma treatment on lung function in children with asthma. *Pulm Pharmacol Ther,* 20**,** 691-700.

STOCKS, J. & GODFREY, S. (1976) The role of artificial ventilation, oxygen and CPAP in the pathogenesis of lung damage in neonates: assessment by serial measurements of lung function. *Pediatrics,* 57**,** 352-362

STOKES, G. M., MILNER, A. D., HODGES, I. G. C. & GROGGINS, R. C. (1981) Lung function abnormalities after acute bronchiolitis. *J Pediatr,* 98**,** 871-874.

STRETTON, M., AJIZIAN, S., MITCHELL, I. & NEWTH, C. (1992) Intensive care course and outcome of patients infected with respiratory syncytial virus. *Pediatr Pulmonol,* 13**,** 143-150.

TASKER, R. C., GORDON, I. & KIFF, K. (2000) Time course of severe respiratory syncytial virus infection in mechanically ventilated infants. *Acta Paediatrica,* 89**,** 938-941.
TELFORD, K., WATERS, L., VYAS, H. G., MANKTELOW, B. N., DRAPER, E. S. & MARLOW, N. (2006) Outcome after neonatal continuous negative-pressure ventilation: follow-up assessment. *Lancet,* 367**,** 1080-1085.
TELFORD, K., WATERS, L., VYAS, H. G., MANKTELOW, B. N., DRAPER, E. S. & MARLOW, N. (2007) Respiratory outcome in late childhood following neonatal continuous negative pressure ventilation. *Arch Dis Child Fetal Neonatal Ed,* 92**,** F19-F24.
THE ARDS NETWORK (2000) Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome. *N Engl J Med,* 342**,** 1301-1308.
THE IMPACT-RSV STUDY GROUP (1998) Palivizumab, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, Reduces Hospitalization From Respiratory Syncytial Virus Infection in High-risk Infants. *Pediatrics,* 102**,** 531-537.
THE INTERNATIONAL STUDY OF ASTHMA AND ALLERGIES IN CHILDHOOD (ISAAC) STEERING COMMITTEE (1998) Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Respir J,* 12**,** 315-335.
THOMSON, A. (1997) The role of negative pressure ventilation. *Arch Dis Child,* 77**,** 454-458.
TIBBY, S. M., HATHERILL, M., WRIGHT, S. M., WILSON, P., POSTLE, A. D. & MURDOCH, I. A. (2000) Exogenous Surfactant Supplementation in Infants with Respiratory Syncytial Virus Bronchiolitis. *Am. J. Respir. Crit. Care Med.,* 162**,** 1251-1256.
TREMBLAY, L., VALENZA, F., RIBEIRO, S. P., LI, J. & SLUTSKY, A. S. (1997) Injurious Ventilatory Strategies Increase Cytokines and c-fos m-RNA Expression in an Isolated Rat Lung Model. *J. Clin. Invest.,* 99**,** 944-952.
VALLETTA, E. A., PIACENTINI, G. L., DEL COL, G. & BONER, A. L. (1997) FEF25-75 as a marker of airway obstruction in asthmatic children during reduced mite exposure at high altitude. *J Asthma,* 34**,** 127-31.
VAN DEN HOOGEN, B. G., DE JONG, J. C., GROEN, J., KUIKEN, T., DE GROOT, R., FOUCHIER, R. A. & OSTERHAUS, A. D. (2001) A newly discovered human pneumovirus isolated from young children with respiratory tract disease. *Nat Med,* 7**,** 719-24.
VAN WOENSEL, J. B., KIMPEN, J. L. L., SPRIKKELMAN, A. B., OUWEHAND, A. & VAN AALDEREN, W. M. C. (2000) Long-term effects of prednisolone in the acute phase of bronchiolitis caused by respiratory syncytial virus. *Pediatr Pulmonol,* 30**,** 92-96.
VENTRE, K. & RANDOLPH, A. G. (2007) Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children.[update of Cochrane Database Syst Rev. 2004;(4):CD000181; PMID: 15494991]. *Cochrane Database Syst Rev***,** CD000181.
VERT, P., ANDRE, M. & SIBOUT, M. (1973) Continuous positive airway pressure and hydrocephalus. *Lancet,* 302**,** 319.
VON NEERGAARD, K. & WIRZ, K. (1927) Die Messung der Stromungswiderstande in den Atemwegen des Menschen, insbesondere bei Asthma und Emphysem. *Z Klin Med,* 105**,** 51-82.

WANG, E., MILNER, R., ALLEN, U. & MAJ, H. (1992) Bronchodilators for treatment of mild bronchiolitis: a factorial randomised trial. *Arch Dis Child.,* 67**,** 289-293.
WANG, E. E., LAW, B. J. & STEPHENS, D. (1995) Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) prospective study of risk factors and outcomes in patients hospitalized with respiratory syncytial viral lower respiratory tract infection. *J Pediatr.,* 126**,** 212-9.
WEBB, M. S. C., HENRY, R. L., MILNER, A. D., STOKES, G. M. & SWARBRICK, A. S. (1985) Continuing respiratory problems three and a half years after acute viral bronchiolitis. *Arch Dis Child,* 60**,** 1064-1067.
WELLIVER, R. C. & DUFFY, L. (1993) The relationship of RSV-specific immunoglobulin E antibody responses in infancy, recurrent wheezing and pulmonary function at age 7-8 years. *Pediatr Pulmonol,* 15**,** 19-27.
WENZEL, S. E., GIBBS, R. L., LEHR, M. V. & SIMOES, E. A. F. (2002) Respiratory outcomes in high-risk children 7 to 10 years after prophylaxis with respiratory syncytial virus immune globulin. *Am J Med,* 112**,** 627-633.
WILLIAMS, J. V., HARRIS, P. A., TOLLEFSON, S. J., HALBURNT-RUSH, L. L., PINGSTERHAUS, J. M., EDWARDS, K. M., WRIGHT, P. F. & CROWE, J. E., JR. (2004) Human Metapneumovirus and Lower Respiratory Tract Disease in Otherwise Healthy Infants and Children. *N Engl J Med,* 350**,** 443-450.
WILSON, N. M., BRIDGE, P. D., PHAGOO, S. B. & SILVERMAN, M. (1995) The measurement of methacholine responsiveness in 5 year old children: three methods compared. *Eur Respir J,* 8**,** 364-370.
WONG, J. Y., MOON, S., BEARDSMORE, C., O'CALLAGHAN, C. & SIMPSON, H. (2000) No objective benefit from steroid inhaler via a spacer in infants recovering from bronchiolitis. *Eur Respir J,* 15**,** 388-394.
WOOD, D. W., DOWNES, J. J. & LECKS, H. I. (1972) A clinical scoring system for the diagnosis of respiratory failure. Preliminary report on childhood status asthmaticus. *Am J Dis Child,* 123**,** 227-228.
WOOD, N. S., MARLOW, N., COSTELOE, K., GIBSON, A. T., WILKINSON, A. R. & THE EPICURE STUDY GROUP (2000) Neurologic and developmental disability after extremely preterm birth. *N Engl J Med,* 343**,** 378-384.
WORLD HEALTH ORGANISATION (1980) International Classification of impairments, disabilities and handicaps (ICIDH-2). Geneva, WHO.
WREN, W. S., MOORE, K. P. & CAHILL, J. (1982) Ventilatory assistance in infants with bronchiolitis. I*r Med J*, 75, 461-2.
YOUNG, S., O'KEEFFE, P., ARNOTT, J. & LANDAU, L. (1995) Lung function, airway responsiveness and respiratory symptoms before and after bronchiolitis. *Arch Dis Child,* 72**,** 16-24.

9 Appendices

9.1 Appendix A: Invitation letter - CNEP cases

Letter to parent

NSH notepaper

Dear [Parent]

There has been a lot of publicity about doctors at the North Staffordshire Hospital using a technique called CNEP (continuous negative extrathoracic pressure) to help small babies with their breathing. Doctors and members of the public asked many questions, so an independent research team in Nottingham are hoping to find the answers.

The researchers need to meet lots of children who have had bronchiolitis to see how healthy they are long after they were treated. They will assess the present health of children treated originally in Stoke with CNEP and children who were treated in Nottingham without CNEP. They will then compare the health of the two groups.

Our records show that your child [Rupert] was treated for bronchiolitis at the North Staffordshire Hospital and had CNEP as part of [his] treatment. The researchers would very much like to meet [Rupert] and many other children like [him].

The research team is based at the University of Nottingham with Professor Neil Marlow in charge. The leaflet with this letter tells you all about Professor Marlow's work and asks for your help. You are being asked to help with a formal research study, but you will see that for [Rupert] it is only a check-up and it will help you find out more about him and CNEP.

Professor Marlow's team want to be sure that the public and the medical profession know about any benefits or problems that came from this use of CNEP, and they hope their work will answer the questions independently and without bias.

You don't have to help Professor Marlow, but we would be grateful if you could tell us whether or not you would like to help. The information leaflet has been written to help you decide. If we do not hear from you, we will write again in a few weeks because we would like to hear from as many people as possible, whatever your views.

Thank you in advance for your reply.

Yours sincerely

[WL]

9.2 Appendix B: Invitation letter - Controls

Letter to parent

QMC notepaper

Dear [Parent]

There has been a lot of publicity about doctors using a technique called CNEP (continuous negative extrathoracic pressure) to help small babies with their breathing. Many doctors and members of the public asked questions – and an independent research team in Nottingham are asking for your help to find some answers.

Doctors at the North Staffordshire Hospital in Stoke used CNEP to help babies with bronchiolitis, the same condition your child [Rupert] was treated for in Nottingham when [he] was a baby. The researchers need to meet lots of children who had bronchiolitis to see how healthy they are long after they were treated. They will assess the present health of children treated originally in Stoke with CNEP and children who were treated in Nottingham without CNEP. They will then compare the health of the two groups.

The research team is based at the University of Nottingham with Professor Neil Marlow in charge. The leaflet with this letter tells you all about Professor Marlow's work and asks for your help. You are being asked to help with a formal research study, but you will see that for [Rupert] it is only a check-up and it will help you find out more about him and CNEP.

Professor Marlow's team want to be sure that the public and the medical profession know about any benefits or problems that came from this use of CNEP, and they hope their work will answer many questions independently and without bias.

You don't have to help Professor Marlow, but we would be grateful if you could tell us whether or not you would like to help. The information leaflet has been written to help you decide. If we do not hear from you, we will write again in a few weeks because we would like to hear from as many people as possible, whatever your views.

Thank you.

Yours sincerely

[HV]

9.3 Appendix C: Parent information leaflet

Helping you decide whether you would like to help us.

We are asking you to take part in our research study, so it is important that you understand why the research is being done and what you would be asked to do. That's what this leaflet is for.

Please read this leaflet carefully. Show it to your friends or family if that helps, or talk it over with your doctor. You can call us if you want to know more or if something we've written isn't clear.

Take your time deciding. You don't have to help us if you don't want to – and even if you decide to help us, you can change your mind at any time and leave our study.

If you don't want to help, or if you change your mind about helping, you will never have to say why.

Whatever you decide, you and your child will always get the best health care possible.

Professor Neil Marlow
Study Director

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This study is sponsored by a grant from NHS Executive (West Midlands).
The grant covers the expenses of the project and the salaries of the research team.

The B-CNEP Study

A long term study of outcome following treatment of bronchiolitis with negative extrathoracic pressure

What is the study for?

Many babies get a lung infection called bronchiolitis, and some of these babies either find it difficult to breathe or may even stop breathing altogether. When this happens, doctors have to choose which way to help the baby breathe. One method is to put a tube into the baby's throat to make it possible to blow air in. This is called intubation. If a machine is connected to this tube and the machine breathes for the baby, this is called ventilation. Even with this help, bronchiolitis often leaves a baby with a wheezy chest. In some this lasts into adult life.

Intubation and ventilation are uncomfortable and can cause problems for the baby. Because of this, doctors at the North Staffordshire Hospital have used another method of helping these babies breathe. They put the baby in a machine that makes a slight vacuum around the baby's chest. The negative pressure of the vacuum takes the pressure off the baby's chest, making it easier for them to breathe. This is called continuous negative extrathoracic pressure, or CNEP. This method is not widely used to help babies with bronchiolitis, in the UK or anywhere else.

Of course everyone wants to know which method is best for the baby, not only while they are in hospital with bronchiolitis but also long after the original treatment. That's why this is called a long-term study – we want to find out which method gives babies the best chance of growing up without breathing troubles. Every new method of helping babies breathe gets a long-term study.

That's why we would like your help. We want to see how well [Rupert] is doing, to see how healthy [he] is compared with lots of other children who also needed help with their breathing. Some of those children were helped by CNEP, some by the other methods. This study will tell us whether CNEP gives babies with bronchiolitis a better chance of growing up strong and healthy.

What will I have to do if we agree to take part?

We will ask you to bring [Rupert] to either Grindley Hill Court (next to the City General Hospital in Stoke on Trent) or the Queen's Medical Centre in Nottingham, so that our paediatrician Dr Yanney can meet [Rupert] and see how well [he] is doing. This will be a medical check-up. We won't be taking blood, giving injections, or doing anything else that hurts.

While you are there, we will ask you to complete a questionnaire. This will ask you what you have noticed about [Rupert]'s general health and behaviour. It will also ask about [Rupert]'s family background, your home and your work, in case this is relevant to [Rupert]'s health. All this will take about 1 hour.

What will happen to [Rupert] in the check-up?
Our paediatrician Dr Yanney will do the medical check up which includes measuring [Rupert's] height and weight. Dr Yanney may also perform an examination on [Rupert] which would include testing [his] movements, coordination and muscle strength– in other words, how well [he] controls [his] arms and legs. Dr Yanney will also listen to [Rupert]'s chest and he will want to see how well [Rupert]'s lungs are working. To do this he will ask [Rupert] to do two breathing tests, one where [he] will be asked to blow hard into a tube and another where [he] will breathe normally through a tube. Then he will give [Rupert] a standard dose of an asthma inhaler called salbutamol. This is given to [Rupert] by asking [him] to breathe in from the inhaler. Afterwards, Dr Yanney will ask [Rupert] to do the breathing tests again to see if the measurements have improved.

Are there any side effects from this drug?
It is rare for a standard inhaled dose of salbutamol to cause any side effects. Side effects can occur if salbutamol is used too often or too much is taken in one go. Because we would be giving [Rupert] a standard dose, we believe the risk of side effects is very low.

Salbutamol is a very common drug for asthma that helps people breathe by opening up their airways. It is often supplied under the brand name Ventolin.

Has anyone else looked at the possible risks?
Ethics committees are an independent group of people (doctors and non-medical people) who think carefully about planned research projects. The ethics committees of the two Regional Health Authorities involved with our study have looked at our plans. They agree that the study is acceptable.

If you would like to know more about medical research, a leaflet called 'Medical Research and You' (published by CERES) is available from North Staffordshire Local Research Ethics Office. We can provide you with a copy of this if you would like one.

Are there any benefits for us if we decide to help?
After the check-up you will get a report that tells you how well [Rupert] has done and when the study is finished you can have a copy of either the main research report or a summary, whichever you prefer. You will be helping parents like yourself and children like [Rupert] in the future, because we will know more about how best to help children with bronchiolitis. We hope that you and [Rupert] will find your time with us interesting and fun. We offer an inconvenience allowance in recognition of the time given to help in our study.

Who will pay for the travel?
We will also refund all reasonable travel costs.

What will you do with all the information?
The information about you and [Rupert] will be seen only by our study team in Nottingham, and we will remove all names before we put anything into a computer. Once we have analysed the information, we will destroy all the original paperwork. When we publish what we have found, we won't mention any child by name.

What do I do next?
If you want to know more, please call us on the number at the bottom of the page.

If you decide not to take part, please send back the form to say so in the envelope provided. Even doing that will be helpful for the study.

If you feel you would like to help us, please fill in and sign the consent form and post it to us in the pre-paid envelope. Our administrator Mrs Heather Palmer will contact you and arrange a date for [Rupert]'s check-up.

Thank you for your interest in our work

9.4 Appendix D: Assessment record

B- CNEP Assessment Record

Office Use Only

Child No. ☐☐☐ Date of Birth ☐☐☐☐☐☐

Chronological Age ☐☐ Years ☐☐ Months

Male ☐ Female ☐ Decimal Age ☐☐ . ☐☐ Years

To Be Completed By Paediatrician

Date of Assessment ☐☐☐☐☐☐

Time Assessment Started ☐☐☐☐ Time Assessment Finished ☐☐☐☐

Others present: Mother ☐ Father ☐ Sibling(s) ☐ Adult friend/Relative ☐

Psychologist ☐ Other children ☐

	Yes	No	*If no, was a second questionnaire given with a freepost envelope?* Yes	No
Parental questionnaire received?	☐	☐	☐	☐
History completed by interview?	☐	☐	☐	☐
If 'No', history received?			☐	☐
Growth	☐	☐		
Lung function	☐	☐	Form Attached	☐
Salbutamol	☐	☐		
Clinical examination	☐	☐		

A. Testers Rating of Child Behaviour

NB Point 1 to be scored immediately; 2-8 to be scored at the end of the assessment.
Please circle the appropriate number.

1. <u>Approach / Withdrawal</u> (Initial reaction)

How wary was the child of the tester? **N/A**

Very withdrawn and shy **1 2 3 4 5 6 7 8 9** Very accepting/ actively approaching **10** ☐

B. Growth and Blood Pressure

"Please take off your shoes."

	Weight	☐ *Kg*	To nearest kilogram	Z- score	☐
	Height	☐ *Cm*	To nearest cm	Z- score	☐
Head circumference		☐ *Cm*	To nearest cm	Normal=0, <C5=1 >C95=2	☐

Blood pressure (Sitting) ☐ *over* ☐ *Mm Hg* *To nearest 2 mm Hg*

systolic *diastolic*

Other – Comment

C. Respiratory Examination

On clinical examination did you observe?

Chronic Signs:

Is the trachea deviated? ☐ (No=0; Yes=1)

Does the child have any chest deformity? ☐ (No=0; Yes=1)

Harrison's sulci ☐ (No=0; Yes=1)

Hyperinflation ☐ (No=0; Yes=1)

Number of chronic signs? ☐ (0-4)

Acute Signs:

Recession ☐ (No=0; Yes=1)

Use of accessory muscles ☐ (No=0; Yes=1)

Auscultation: crackles ☐ (No=0; Yes=1)

Wheezes ☐ (No=0; Yes=1)

Number of acute signs? ☐ (0-4)

What was the resting respiratory rate? (over 30 seconds) ☐ *Breaths/min*

.

D. Lung Function Tests

1. Rint

Sitting, 5 measurements in expiration, at tidal volume

2. Spirometry

Standing,
Use incentive,
Encourage maximum effort
Record best of 3

Record:

- ❑ PRE
- ➢ M-R_{int} median
- ➢ FEV_1
- ➢ FEV_1 % predicted
- ➢ FVC
- ➢ FVC % predicted
- ➢ FEF25-75

• *Salbutamol via spacer:*

15 minute break

- ❑ POST
- ➢ M-R_{int} median
- ➢ FEV_1
- ➢ FEV_1 % predicted
- ➢ FVC
- ➢ FVC % predicted
- ➢ FEF25-75

Salbutamol:

Dose: _____ puffs (100μg per puff) of salbutamol via spacer

Prescribed by _____ Given by _____ Date _____
Time_____

Was lung function adequately performed Yes[1] ☐ No[0] ☐ ☐

Was lung function repeated after salbutamol Yes[1] ☐ No[0] ☐ ☐

If unable to perform lung function tests, please state why:

Tracheostomy[1] ☐ Unable to cooperate[2] ☐

Parent request[3] ☐ Other[4] ☐

Other, please state _____ ☐

Attatch micro-Rint and spirometry data sheets to this page.

E. Neurological Examination

1. Axis

Normal axis control? Yes[1] ☐ No[0] ☐ ☐

If yes, go to question 2. If no, complete this section.

Head control	*(Abnormal but head up for extended periods=1; Poor, holds head up only for short periods=2; No control=3)*	☐
Truncal tone	*(Extensor predominant=1; opisthotonus=2; hypotonia=3)*	☐
Sitting	*(Can sit but less secure than normal=1; Cannot be left unsupported=2; Difficult to place in sitting position (any reason)=3)*	☐

Other –comment

2. Abnormal movements on observation

Movements observed (most prominent sign)	*At rest*	*With goal direction or excitement*
None	☐ *0*	☐
Incoordination	☐ *1*	☐
Tremor	☐ *2*	☐
Short and jerky	☐ *3*	☐
Slow and writhing	☐ *4*	☐
Flexor/Extensor spasms	☐ *5*	☐
	☐	☐

Comment

3. Upper Limb

			Left		Right	
A	Tone	*Increased=1; Decreased=2; Variable=3*	☐		☐	
	Tendon Jerks Biceps, Triceps, Supinator (Record the worst score)	*Absent=1; Increased=2; >3 beats clonus=3*	☐		☐	
		State worst tendon Sup=1, BC=2, TC=3	☐		☐	
B	Asymmetry	*Tick the side with highest tone ≥1 grade or ≥ 10° passive tone difference*	☐	**OR**	☐	*L=1, R=2* ☐

If the above are all normal continue to lower limb. If any abnormality complete section C.

C	Scarf	*(AAL-ML=1; <AAL=2)*	☐		☐
	Adducted thumb	*(Present=1)*	☐		☐
	Wasting	*(Present=1)*	☐		☐
	Fisting	*(Present=1)*	☐		☐

Abnormalities in section A (no=0, 1=1, >1=2) ☐

Abnormalities in section C (no=0, yes=1) ☐

Comment

Upper Limb Function

(clarify with carer if necessary)

Normal function, no impairment ☐ 0

Impairment, e.g. loss of a digit, but normal function ☐ 1

Mild clumsiness, but independent ☐ 2

Able to feed and dress self but requires aids or assistance for some tasks, eg feeding and dressing ☐ 3

Severe difficulty with fine movements, requires aids or assistance for feeding and dressing ☐ 4

☐

4. Lower Limb

			left	*right*	
A	Tone	*increased=1 decreased=2 variable=3*			
Ankle stretch		*Phasic=1 tonic or clonus= 2*			
Tendon jerks (record the worst score)		*absent=1 increased=2 >3 beats clonus=3*			
		State which tendon (KJ=1, AJ=2)			
Plantar response		*normal=0 equivocal=1 persistently up=2*			
B	Asymmetry	*(≥1 grade or ≥10° passive tone difference) Tick the side with the highest tone*			*L=1, R=2* ☐

If the above are all normal go to gross motor classification. If any abnormality, complete section C.

C	Heel ear angle (angle between bed &	*>100°=0 90-100°=1 <90°=2*		
Popliteal angle (flex knees and hips, straighten knee)		*>110=0° 100-110=1° <100=2°*		
Ankle angle (angle between foot and shin)		*<80°=0 80-90°=1 >90°=2*		
Adductor angle "Pretend to be a pair of scissors"		*>110°=0 40-110°=1 <40°=2*		
Wasting		*None=0, Present=1*		

Abnormalities in section A (no=0, 1=1, >1=2) ☐

Abnormalities in section C (no=0, yes=1) ☐

Comment

5. Rombergs

Abnormal movements already noted Yes[1] ☐ No[0] ☐

If No, do Rombergs. If Yes, continue to section H.
Instructions: Now stand up and stand as still as you can with your eyes closed and your arms out like this: (arms out in front, palms down),

Normal	☐ 0
Eyes closed; proximal involuntary movements	☐ 1
Eyes closed; distal involuntary movements	☐ 2
Eyes open; proximal involuntary movements	☐ 3
Eyes open; distal involuntary movements	☐ 4
Cannot stand	☐ 5

☐

Other/Reason for being unable to stand

Gross motor function classification system

Level 0	Normal	☐ *0*
Level 1	Walk without restrictions, climb stairs without limitations, can run and jump but with reduced speed, balance, coordination.	☐ *1*
Level 2	Can walk on flat surfaces, climb stairs with rail, limitations on uneven surfaces, inclines, in crowds or confined spaces. Minimal ability in running, jumping.	☐ *2*
Level 3	Walk on level surface with assistive mobility device. Climb stairs using railing. Depending on upper limb function may propel wheelchair manually.	☐ *3*
Level 4	Adaptive seating for trunk control and to maximise hand function. Require assistance or stable surface to move out of chair. Walk short distances with assistance. Self mobility using powered wheelchair.	☐ *4*
Level 5	No independence in basic antigravity postural control. Independent mobility only by power wheelchair with extensive adaptations.	☐ *5*

☐

Neurology Summary

Abnormality

Axis: any abnormality = abnormal.
Limbs: single box abnormal in section A, (either UL or LL)=suspect,
more than one box abnormal in section A (UL or LL) or any abnormality in section C=abnormal.

Normal=0, suspect=1, abnormal=2 ☐ *If normal or suspect, go to section H: HUI*

Distribution

Lower limbs worse than upper ☐ *1*

Upper limbs worse than lower limbs ☐ *2*

All limbs equally impaired ☐ *3* ☐

Asymmetry? ☐ *Present=1, not=0*

Dyskinesia? ☐ *Present=1, not=0*

Type of movement disorder:

Cerebral Palsy *1* ☐ Generalised Hypotonia ☐ Other *3* ☐ ☐

Cerebral Palsy: definitions in coding sheet.

If cerebral palsy present, classify:

Bilateral Spastic[1] ☐ Dystonic[3] ☐ Ataxic[5] ☐

Spastic Hemi[2] ☐ Choreoathetotic[4] ☐ ☐

F. Vision

Is there a visual or eye defect of any type present?

No abnormality [0] Yes- Right eye only [1] Yes- Left eye only [2] Yes- Both eyes [3]

Usual vision (with spectacles if worn)

Normal or near normal [0]

Impaired but appears to have useful vision [1]

Sees light or gross movement only [2]

No useful vision (blind). [3]

Is there a squint present (manifest) Yes[1] No[0]

Are there abnormal eye movements present Yes[1] No[0]

Does the child have a problem with fixation Yes[1] No[0]

Does the child have a problem with tracking Yes[1] No[0]

Abnormality of any of the above? (Y=1, N=0)

Other – Comment

G. Hearing

Is there a hearing impairment of any type Yes [1] No [0]

Usual hearing (with aids if worn)

Normal or near normal [0]

Hearing loss corrected with aids [1]

Some hearing but loss not corrected with aids [2]

No useful hearing even with aids [3]

Other – Comment

H. HUI-3

These are questions about the child's usual health and usual ability to do things. Please do not report temporary or occasional problems.

1. Which <u>one</u> of the following best describes the child's usual ability to see well enough to read ordinary newsprint?

- Able to see well enough without glasses or contact lenses ☐
- Able to see well enough with glasses or contact lenses ☐
- Unable to see well enough even with glasses or contact lenses ☐
- Unable to see at all ☐ ☐

2. Which <u>one</u> of the following best describes the child's usual ability to see well enough to recognise a friend on the other side of the street?

- Able to see well enough without glasses or contact lenses ☐
- Able to see well enough with glasses or contact lenses ☐
- Unable to see well enough even with glasses or contact lenses ☐
- Unable to see at all ☐ ☐

3. Which <u>one</u> of the following best describes the child's usual ability to hear what is said in a group conversation with at least three other people?

- Able to hear what is said without a hearing aid ☐
- Able to hear what is said with a hearing aid ☐
- Unable to hear what is said even with a hearing aid ☐
- Unable to hear what is said, but doesn't wear a hearing aid ☐
- Unable to hear at all ☐ ☐

4. Which <u>one</u> of the following best describes the child's usual ability to hear what is said in a conversation with one other person in a quiet room?

- ☐ Able to hear what is said without a hearing aid
- ☐ Able to hear what is said with a hearing aid
- ☐ Unable to hear what is said even with a hearing aid
- ☐ Unable to hear what is said, but doesn't wear a hearing aid
- ☐ Unable to hear at all

5. Which <u>one</u> of the following best describes the child's usual ability to be understood when speaking his/her own language with people who do not know him/her?

- ☐ Able to be understood completely
- ☐ Able to be understood partially
- ☐ Unable to be understood
- ☐ Unable to speak at all

6. Which <u>one</u> of the following best describes the child's usual ability to be understood when speaking with people who know him/her well?

- ☐ Able to be understood completely
- ☐ Able to be understood partially
- ☐ Unable to be understood
- ☐ Unable to speak at all

7. Which <u>one</u> of the following best describes how the child usually feels?

Happy and interested in life	☐	
Somewhat happy	☐	
Somewhat unhappy	☐	
Very unhappy	☐	
So unhappy that life is not worthwhile	☐	☐

8. Which <u>one</u> of the following best describes the child's usual level of pain and discomfort?

Free of pain and discomfort	☐	
Mild to moderate pain or discomfort that prevents no activities	☐	
Moderate pain or discomfort that prevents some activities	☐	
Moderate to severe pain or discomfort that prevents some activities	☐	
Severe pain or discomfort that prevents most activities	☐	☐

9. Which <u>one</u> of the following best describes the child's usual ability to walk?

Note: walking equipment refers to mechanical supports such as braces, crutches or a walker.

Able to walk around the neighbourhood without difficulty, and without walking equipment	☐	
Able to walk around the neighbourhood with difficulty, but does not require walking equipment or the help of another person	☐	
Able to walk around the neighbourhood with walking equipment, but without the help of another person	☐	
Able to walk only short distances with walking equipment, and requires a wheelchair to get around the neighbourhood	☐	
Unable to walk alone, even with walking equipment. Able to walk short distances with the help of another person, and requires a wheelchair to get around the neighbourhood	☐	
Unable to walk at all	☐	☐

10. Which <u>one</u> of the following best describes the child's usual ability to use his/her hands and fingers?

Note: Special tools refers to hooks for buttoning clothes, gripping devices for opening jars or lifting small items, and other devices to compensate for limitations of hands or fingers.

Full use of two hands and ten fingers ☐

Limitations in the use of hands or fingers, but does not require special tools or the help of another person ☐

Limitations in the use of hands or fingers, independent with use of special tools (does not require the help of another person) ☐

Limitations in the use of hands or fingers, requires the help of another person for some tasks (not independent even with use of special tools) ☐

Limitations in use of hands or fingers, requires the help of another person for most tasks (not independent even with the use of special tools) ☐

Limitations in use of hands or fingers, requires the help of another person for all tasks (not independent even with use of special tools) ☐ ☐

11. Which <u>one</u> of the following best describes the child's usual ability to remember things?

Able to remember most things ☐

Somewhat forgetful ☐

Very forgetful ☐

Unable to remember anything at all ☐ ☐

12. Which <u>one</u> of the following best describes the child's usual ability to think and solve day to day problems?

Able to think clearly and solve day to day problems ☐

Has a little difficulty when trying to think and solve day to day problems ☐

Has some difficulty when trying to think and solve day to day problems ☐

Has great difficulty when trying to think and solve day to day problems ☐

Unable to think or solve day to day problems ☐ ☐

13. Which <u>one</u> of the following best describes the child's usual ability to perform basic activities?

Eats, bathes, dresses and uses the toilet normally	☐
Eats, bathes, dresses or uses the toilet independently with difficulty	☐
Requires mechanical equipment to eat, bathe, dress or use the toilet independently	☐
Requires the help of another person to eat, bathe, dress or use the toilet	☐

14. Which <u>one</u> of the following best describes how the child usually feels?

Generally happy and free from worry	☐
Occasionally fretful, angry, irritable, anxious or depressed	☐
Often fretful, angry, irritable, anxious or depressed	☐
Almost always fretful, angry, irritable, anxious or depressed	☐
Extremely fretful, angry, irritable or depressed, to the point of needing professional help	☐

15. Which <u>one</u> of the following best describes the child's usual level of pain or discomfort?

Free of pain and discomfort	☐
Occasional pain or discomfort. Discomfort relieved by non-prescription drugs or self-control activity without disruption of normal activities	☐
Frequent pain or discomfort. Discomfort relieved by oral medicines with occasional disruption of normal activities	☐
Frequent pain or discomfort. Frequent disruption of normal activities. Discomfort requires prescription narcotics (eg morphine) for relief.	☐
Severe pain or discomfort. Pain not relieved by drugs and constantly disrupts	☐

A(2). Tester's Ratings of Child Behaviour

Complete at the end of the assessment. Please circle the appropriate number.

Attention Span

How long does the child continue and persist in solving the task?

V. brief periods/v. short attention span/no directed effort or absorption **1 2 3 4 5 6 7 8 9** V. long periods/long attention span / v. persistent and absorbed **10** ☐

Robustness and Endurance

Energy resource available to the child during the testing period.

V. fragile / v. little energy / tires easily **1 2 3 4 5 6 7 8 9** V. robust, good energy sources **10** ☐

Social Attractiveness

How appealing is the child to interact with?

V. little initiating social interaction, tester glad to be finished **1 2 3 4 5 6 7 8 9** V. rewarding social partner. Enjoyable to "take home" **10** ☐

Demandingness (Need for facilitation)

How much encouragement does the child require?

Little need for facilitation. Child well organised. Little work for tester **1 2 3 4 5 6 7 8 9** Great need for facilitation. V. hard work for examiner, demanding **10** ☐

General Emotional Tone (Mood)

Very unhappy throughout **1 2 3 4 5 6 7 8 9** Very happy / never upset **10** ☐

Cooperativeness

Cooperation with the tester and complies with requests

Very resisting / uncooperative **1 2 3 4 5 6 7 8 9** V. cooperative/ readily enthusiastically enters suggested tasks / games **10** ☐

Difficultness

Overall impression of the difficultness of the child

Very easy **1 2 3 4 5 6 7 8 9** Very difficult **10** ☐

I. Classification of Disability

	Cognitive (I)	Motor (M)	Vision (V)	Hearing (H)	Behaviour (B)	Other (O)
Normal	**0**	**0**	**0**	**0**	**0**	**0**
Impairment/ Mild	**1**	**1**	**1**	**1**	**1**	**1**
Moderate/ Severe	**2**	**2**	**2**	**2**	**2**	**2**

	Cognitive	Motor	Vision	Hearing	Behaviour	Other
Domain Number	**1**	**2**	**3**	**4**	**5**	**6**
Score (0-2)	☐	☐	☐	☐	☐	☐

Worst Score ☐ **Domain Number** ☐

Feedback Letter

We will translate this form into a letter for the parents/carers.

CHILD'S NAME:

General comment:

We found [child's name] to be a…….…… participant.
(Insert short, positive statement e.g. Happy, friendly etc.)

Weight: _____ **kgs** **Centiles** _____

Height: _____ **Cm** **Centiles** _____

Head Circumference: _____ **Cm** **Centiles** _____

(State if a measurement is on, below or above a centile)

Lung function Normal ☐ Below normal ☐

Blood Pressure Normal ☐ Raised ☐

We will give you a letter to give to your doctor ☐ Tick if applicable

Physical Disabilities (*Please describe e.g. cerebral palsy, visual /hearing loss)*

Any other comments:

Check list

Ensure that you have completed all parts and attached lung function forms.

1. Parental questionnaire
2. Medical history sheet
3. Child QoL questionnaire
4. Assessment (this form)

- Growth
- Clinical examination and impairments
- Lung function*
- Parent feedback form

***Attach record sheet**

Completed By _____

Signed _____

Date _____

9.5 Appendix E: Medical history questionnaire

The B-CNEP Study

Medical History Interview Record

In this questionnaire we ask you for some important details about the health of your child, and a few questions about your home.

Office Use Only:

Name

Study Number

Date

Entry 1

Entry 2

A. Long-term Illness

1. **Does your child have *any* long-term illness or impairment?** No ☐ 0

If no, go to question 2. If yes, please list and give details: Yes ☐ 1 ☐

_____

_____

_____

_____

2. Over the last 12 months, how many days of school has your child missed through any illness?

Because of a chest problem ☐ Days

Fits or other neurological problem ☐ Days Office

Other problem ☐ Days N ☐

T ☐

B. Hospital admissions

1a. **In the last 12 months, has your child been admitted for breathing difficulties? (E.g. asthma, wheezing, respiratory infections).** No ☐

Yes ☐

1b. **If yes:**

Age	**Condition**	**Hospital**	**Approx stay (Days)**

N ☐

T ☐

2a. **In the last 12 months, has he/she been admitted for surgery?** No ☐

Yes ☐

2b. **If yes:**

Age	**Condition**	**Hospital**	**Approx stay (Days)**

N ☐

T ☐

3a. In the last 12 months, has he/she been admitted to hospital for any other reasons? E.g. Fits, gastroenteritis

No ☐
Yes ☐

3b. If yes:

Age	Condition	Hospital	Approx stay (Days)

Office Use

N ☐☐
T

4a. Has he/she <u>ever</u> been admitted to an intensive care unit?

No ☐
Yes ☐

4b. If yes:

Age	Condition	Hospital	Approx stay (Days)

N ☐☐
T

C. Chest Problems

1a. In the last 12 months, has your child had wheezing or whistling

No[0] ☐ Yes[1] ☐

Office Use ☐

If no, please go to question 2 (on the next page).
If yes, please continue below.

1b. In the last 12 months, how many attacks of wheezing has your child had?

None ☐ [0] 1 to 3 ☐ [1] 4 to 12 ☐ [2] More than 12 ☐ [3] ☐

1c. In the last 12 months, how often has your child's sleep been disturbed due to wheezing?

Never woken[0] ☐ Less than one night per week[1] ☐ One or more nights per week[2] ☐ ☐

1d. In the last 12 months, has wheezing ever been severe enough to limit your child's speech to only 1 or 2 words between breaths?

No[0] ☐ Yes[1] ☐ ☐

2. **Has any doctor <u>ever</u> said that your child has asthma?** No[0] ☐ Yes[1] ☐ ☐

3. **In the last 12 months, has your child's chest sounded wheezy during or after exercise?** No[0] ☐ Yes[1] ☐ ☐

4. **In the last 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or a chest infection?** No[0] ☐ Yes[1] ☐ ☐

5. **In the last 12 months, has your child seen a paediatrician or chest specialist about a chest or breathing problem?** No[0] ☐ Yes[1] ☐ ☐

6. **In the last 12 months, has your child been treated for any respiratory or chest problems?** No[0] ☐ Yes[1] ☐ ☐

7. **Please indicate which *chest* medications or inhalers your child is currently taking.**
We will ask you about other medications later on.

None		☐ 0
Prednisolone (oral)		☐ 1
Home Oxygen		☐ 2
Inhalers		
Relievers	Ventolin (blue)	☐ 3
	Bricanyl (blue)	☐ 3
	Atrovent (white)	☐ 4
Salmeterol (green) or other reliever		☐ 5
Preventers	Any steroid inhaler	☐ 6

8. **If your child is taking a steroid inhaler, please state which one:**
e.g. Becotide (brown), Pulmicort (brown), Flixotide (orange)

_____

Office Use ☐☐☐☐☐☐☐

9. **Please state any medicines or inhalers taken today.**

_____ None 0 ☐

_____ Short 1 ☐

_____ Long 2 ☐

D. Neurological Problems

1. In the last 2 years, has your child had a fit or seizure? No[0] ☐
Yes ☐

If no, please go to question 3.

If yes, when was the last fit/seizure?

Last 1 month[3] ☐ Last 6 months[2] ☐ Over 6 months ago[1] ☐ ☐

2. Have you been given regular medicine to control your child's fits? No[0] ☐
If yes, please give details: Yes[1] ☐ ☐

Medication	Treatment continuing	Treatment stopped
_____	☐	☐
_____	☐	☐
_____	☐	☐
_____	☐	☐

3a. Has your child ever had hydrocephalus? Yes ☐
No0 ☐

3b. If yes, has your child ever had a shunt to treat this? Yes2 ☐
No1 ☐ ☐

E. Medications

10. Is your child *currently* on any medicines not already mentioned? No[0] ☐
Yes[1] ☐ ☐

If no, go to section D (overleaf).
If yes, please specify:
e.g. Ritalin (methylphenidate)

_____

_____

F. Your Home

The following questions apply to your home and your family, by this we mean mum (or partner), dad (or partner) and brothers and sisters.

		0		1	*Office*
1a. Do you have any long-haired or feathered pets at home?	No	☐	Yes	☐	E

1b. If the answer to 18 is *Yes*, please specify: cats/dogs/birds etc. _____

2. Does your house have problems with damp?	No	☐	Yes	☐	E
3. Does your house have problems with mould on the walls?	No	☐	Yes	☐	E
4. Have any members of your family had any attacks of wheezing or whistling in the chest?	No	☐	Yes	☐	I
5. Has a doctor ever said that any member of your family has asthma?	No	☐	Yes	☐	I
6. Has any member of your family ever had hay fever?	No	☐	Yes	☐	I
7. Apart from asthma have you or any of the household had any long-term chest problems since your child was born?	No	☐	Yes	☐	I

Office- E: (0-3) ☐ *I:(0-4)* ☐

G. Smoking

1. Does anyone in the household smoke? No[0] ☐ Yes[1] ☐

If yes, please state who: Parent(s)[1] ☐ Sibling[1] ☐ Study child[2] ☐ Other[1] ☐ ☐

2. Does your child have contact (more than 15 hrs a week) with friends, family or childminders who smoke? No[0] ☐ Yes[1] ☐ ☐

Question 3 applies to the child's mother:

3. Did you smoke whilst you were pregnant with this child?

Not applicable[9] ☐ No[0] ☐ Yes[1] ☐ ☐

Name of person giving history _____

Relationship to child _____

Interviewer _____

Interviewer's Signature _____

Date _____

If you completed this form without an interviewer present, please sign here: _____

9.6 Appendix F: Parental questionnaire

The B-CNEP Study

Parental questionnaire about your home and family, and your child.

In this questionnaire we ask you for some important details about your home and family and

Please complete the questions in this booklet as accurately as possible. If you have any questions, or need any help, please telephone us on:

(0115) 924 9924 extension 43358

Office Use Only:

Name

Study Number

Date

Entry 1

Entry 2

A. Your Home and Your Family

These questions apply to your house and the family at home, by this we mean mum (or partner), dad (or partner) and brothers and sisters of the child in the study. Please answer all questions that apply to you and your partner.

1. How many children (age up to 18 years) are there in the household (*including* the child taking part in the study)?

		Children

Please list the names and dates of birth of the children.
(You do not need to include details for the child we are assessing today).

NAME	DATE OF BIRTH e.g. 24/06/1994

Home Environment

Please tick the relevant box.

2. Do you rent or own your accommodation?

Owner (mortgage)	☐	
Council rented	☐	
Private rented (furnished)	☐	
Private rented (unfurnished)	☐	
Housing society or co-operative	☐	
Tied to occupation	☐	*Office Use*
Other (please describe below)	☐	☐

_____

3. How many rooms are there in your home?

(Do not count bathrooms. Do not count the kitchen unless used for family meals).

☐☐ *rooms*

4. Do you have the use of a car (including minibus, van etc.)?	No ☐	☐
	Yes ☐	☐
5. Does your partner have the use of a separate car/van etc?	No ☐	☐
	Yes ☐	☐

About You

6. Please tell us your relationship to the child in the study:

Mother	☐	Step-Mum	☐
Father	☐	Step-Dad	☐
Other	☐		☐

If 'other', please specify, e.g. grandmother _____

7. Please tell us who your child lives with:

Mother and Father	☐	Mother and step-Dad	☐	
Mother	☐	Father and step-Mum	☐	
Father	☐	Legal guardian	☐	☐

Other (please specify) _____

8. Do any other adults live with you? Yes ☐ No ☐

(Please only state adults not mentioned above)

If yes, please state how many. ☐☐ *Office Use: A=* ☐

9a. Are you currently

		9b. If you are single, have you previously been		
Single?	☐			
Married?	☐	Widowed?	☐	
Living together?	☐	Separated or divorced?	☐	
Not applicable (I am not a parent of the study child)	☐	None of the above	☐	☐

10. What is your current age?	☐☐ Years	Not applicable	☐	☐
11. What is your partner's current age?	☐☐ Years	Not applicable	☐	☐

Education

This question applies to the mother (or step mother) of the study child.

12. Please state your highest qualification from school or college.

Not applicable ☐

No qualification ☐

Vocational qualification or CSE ☐

O-level or GCSE or Scottish Standards ☐

A-levels or Highers ☐

Nursing Qualification ☐

Teacher Training Qualification ☐

University Degree ☐ ☐

Other qualification after A-level ☐ ☐

If 'other' please describe: _____

This question applies to the father (or step father) of the study child.

13. Please state your highest qualification from school or college.

Not applicable ☐

No qualification ☐

Vocational qualification or CSE ☐

O-level or GCSE or Scottish Standards ☐

A-levels or Highers ☐

Nursing Qualification ☐

Teacher Training Qualification ☐

University Degree ☐ ☐

Other qualification after A-level ☐ ☐

If 'other' please describe: _____

Employment

Questions 14- 19 apply to the mother (or step mother) of the study child.

Office Use

14. Are you in paid employment? No ☐ Yes ☐

Not applicable ☐

15. Current/last occupation: _____

16. Industry: _____

17. How many hours do you work per week? ☐☐ Hours ☐

18. Are you a:

Manager? ☐

Supervisor? ☐

Trainee/Student? ☐

None of the above? ☐

Please describe: _____

19. Are you self-employed? No ☐ Yes ☐ ☐

These questions apply to the father (or step father) of the study child.

20. Are you in paid employment? No ☐ Yes ☐ ☐

21. Current/last occupation: _____

22. Industry: _____

23. How many hours do you work per week? ☐☐ Hours ☐

24. Are you a:

Manager?? ☐

Supervisor? ☐

Trainee/Student? ☐

None of the above? ☐

Please describe: _____

25. Are you self-employed? No ☐ Yes ☐ ☐

Benefits

20. Please indicate which benefits you or your partner receive:
(Tick all that apply)

Child Benefit ☐

Family Credit / Child Tax Credit / Working Family Tax ☐

Invalid Care Allowance / Carers Allowance ☐

Income Support ☐

Job Seekers Allowance ☐

Disability Living Allowance ☐

Incapacity Benefit ☐

Housing Benefit ☐

None of the above ☐

Other ☐

If 'other', please describe:

Office Use ☐☐

B. Your Child's Health

When answering the following questions, please think about your child's usual health and ability to do things on a day-to-day basis. Please do not report the effect of short illnesses such as colds. Focus your answers on your child's abilities, disabilities and how he or she usually feels. You may think that some of these questions do not apply to your child, but it is important that we ask everyone the same questions. Also, a few questions are very similar: please excuse this- we would like you to answer each question independently. Please read each question and consider your answer carefully. For each question, select one answer that best describes your child's usual level of ability or disability. Please indicate the selected answer by ticking the box beside the answer. There are no right or wrong answers. All we would like is your opinion about your child's health.

1. Which one of the following best describes your child's usual ability to see well enough to read ordinary newsprint?

Able to see well enough without glasses or contact lenses ☐

Able to see well enough with glasses or contact lenses ☐

Unable to see well enough even with glasses or contact ☐

Unable to see at all ☐ ☐

2. Which one of the following best describes your child's usual ability to see well enough to recognise a friend on the other side of the street?

Able to see well enough without glasses or contact lenses ☐

Able to see well enough with glasses or contact lenses ☐

Unable to see well enough even with glasses or contact lenses ☐

Unable to see at all ☐ ☐

3. Which one of the following best describes your child's usual ability to hear what is said in a group conversation with at least three other people?

Able to hear what is said without a hearing aid ☐

Able to hear what is said with a hearing aid ☐

Unable to hear what is said even with a hearing aid ☐

Unable to hear what is said, but doesn't wear a hearing aid ☐

Unable to hear at all ☐ ☐

4. Which one of the following best describes your child's usual ability to hear what is said in a conversation with one other person in a quiet room?

Able to hear what is said without a hearing aid ☐

Able to hear what is said with a hearing aid ☐

Unable to hear what is said even with a hearing aid ☐

Unable to hear what is said, but doesn't wear a hearing aid ☐

Unable to hear at all ☐ ☐

5. Which one of the following best describes your child's usual ability to be understood when speaking his/her own language with people who do not know him/her?

Able to be understood completely ☐

Able to be understood partially ☐

Unable to be understood ☐

Unable to speak at all ☐

6. Which one of the following best describes your child's usual ability to be understood when speaking with people who know him/her well?

Able to be understood completely ☐

Able to be understood partially ☐

Unable to be understood ☐

Unable to speak at all ☐

7. Which one of the following best describes how your child usually feels?

Happy and interested in life ☐

Somewhat happy ☐

Somewhat unhappy ☐

Very unhappy ☐

So unhappy that life is not worthwhile ☐

8. Which one of the following best describes your child's usual level of pain and discomfort?

Free of pain and discomfort ☐

Mild to moderate pain or discomfort that prevents no activities ☐

Moderate pain or discomfort that prevents some activities ☐

Moderate to severe pain or discomfort that prevents some activities ☐

Severe pain or discomfort that prevents most ☐ ☐

9. Which one of the following best describes your child's usual ability to walk?

Note: walking equipment refers to mechanical supports such as braces, a cane, crutches or a walker.

Able to walk around the neighbourhood without difficulty, and without walking equipment ☐

Able to walk around the neighbourhood with difficulty, but does not require walking equipment or the help of another person ☐

Able to walk around the neighbourhood with walking equipment, but without the help of another person ☐

Able to walk only short distances with walking equipment, and requires a wheelchair to get around the neighbourhood ☐

Unable to walk alone, even with walking equipment. Able to walk short distances with the help of another person, and requires a wheelchair to get around the neighbourhood ☐

Unable to walk at all ☐ ☐

10. Which one of the following best describes your child's usual ability to use his/her hands and fingers?

Note: Special tools refers to hooks for buttoning clothes, gripping devices for opening jars or lifting small items, and other devices to compensate for limitations of hands or fingers.

Full use of two hands and ten fingers ☐

Limitations in the use of hands or fingers, but does not require special tools or the help of another person ☐

Limitations in the use of hands or fingers, independent with use of special tools (does not require the help of another person) ☐

Limitations in the use of hands or fingers, requires the help of another person for some tasks (not independent even with use of special tools) ☐

Limitations in use of hands or fingers, requires the help of another person for most tasks (not independent even with the use of special tools) ☐

Limitations in use of hands or fingers, requires the help of another person for all tasks (not independent even with use of special tools) ☐ ☐

11. Which one of the following best describes your child's usual ability to remember things?

Able to remember most things ☐

Somewhat forgetful ☐

Very forgetful ☐

Unable to remember anything at all ☐ ☐

12. Which one of the following best describes your child's usual ability to think and solve day to day problems?

Able to think clearly and solve day to day problems ☐

Has a little difficulty when trying to think and solve day to day problems ☐

Has some difficulty when trying to think and solve day to day problems ☐

Has great difficulty when trying to think and solve day to day problems ☐

Unable to think or solve day to day problems ☐ ☐

13. Which one of the following best describes your child's usual ability to perform basic activities?

- Eats, bathes, dresses and uses the toilet normally ☐
- Eats, bathes, dresses or uses the toilet independently with difficulty ☐
- Requires mechanical equipment to eat, bathe, dress or use the toilet independently ☐
- Requires the help of another person to eat, bathe, dress or use the toilet ☐ ☐

14. Which one of the following best describes how your child usually feels?

- Generally happy and free from worry ☐
- Occasionally fretful, angry, irritable, anxious or depressed ☐
- Often fretful, angry, irritable, anxious or depressed ☐
- Almost always fretful, angry, irritable, anxious or depressed ☐
- Extremely fretful, angry, irritable or depressed, to the point of needing professional help ☐ ☐

15. Which one of the following best describes your child's usual level of pain or discomfort?

- Free of pain and discomfort ☐
- Occasional pain or discomfort. Discomfort relieved by non-prescription drugs or self-control activity without disruption of normal activities. ☐
- Frequent pain or discomfort. Discomfort relieved by oral medicines with occasional disruption of normal activities. ☐
- Frequent pain or discomfort. Frequent disruption of normal activities. Discomfort requires prescription narcotics (eg morphine) for relief. ☐
- Severe pain or discomfort. Pain not relieved by drugs and constantly disrupts normal activities. ☐ ☐

C. Your Child's Activities and School

Please fill out this section to reflect your view of your child's behaviour, even if other people might not agree. Feel free to print additional comments beside each item and in the spaces provided.

1. Please list the sports your child most likes to take part in.

For example: swimming, baseball, skating, skateboarding, bike riding, fishing, etc.

Compared to others of the same age, about how much time does he/she spend in each?

Compared to others of the same age, how well does he/she do each one?

Sport	Don't Know	Less Than Average	Average	More Than Average	Don't Know	Less Than Average	Average	More Than Average
a. _____	☐	☐	☐	☐	☐	☐	☐	☐
b. _____	☐	☐	☐	☐	☐	☐	☐	☐
c. _____	☐	☐	☐	☐	☐	☐	☐	☐
None ☐		☐						☐

2. Please list your child's favourite hobbies, activities and games other than sports.

For example: stamps, dolls, books, piano, crafts, cars, singing etc. (Do not include listening to the radio or TV).

Compared to others of the same age, about how much time does he/she spend in each?

Compared to others of the same age, how well does he/she do each one?

Hobby	Don't Know	Less Than Average	Average	More Than Average	Don't Know	Less Than Average	Average	More Than Average
a. _____	☐	☐	☐	☐	☐	☐	☐	☐
b. _____	☐	☐	☐	☐	☐	☐	☐	☐
c. _____	☐	☐	☐	☐	☐	☐	☐	☐
None ☐								☐

3. Please list any organisations, clubs, teams, or groups your child belongs to.
Compared to others of the same age, how active is he/she in each?

Group	Don't Know	Less Than Average	Average	More Than Average
a. _____	☐	☐	☐	☐
b. _____	☐	☐	☐	☐
c. _____	☐	☐	☐	☐
None ☐		☐		

4. Please list any jobs or chores your child has.

For example: paper route, babysitting, making bed, working in store, etc. (Include both paid and unpaid jobs and chores.)

Compared to others of the same age, how well does he/she carry them out?

Job	Don't Know	Less Than Average	Average	More Than Average
a. _____	☐	☐	☐	☐
b. _____	☐	☐	☐	☐
c. _____	☐	☐	☐	☐
None ☐			☐	

5. About how many friends does your child have?
(Do not include brothers and sisters.)

None ☐ 1 ☐ 2 or 3 ☐ 4 or more ☐

6. About how many times a week does your child do things with friends outside of regular school hours? (Do not include brothers and sisters.)

Less than 1 ☐ 1 or 2 ☐ 3 or more ☐

7. Compared to others of his/her age, how well does your child:

	Worse	About average	Better	Has no brothers or sisters
Get along with brothers and sisters?	☐	☐	☐	☐
Get along with other kids?	☐	☐	☐	
Behave with his/her parents?	☐	☐	☐	
Play and work alone?	☐	☐	☐	

8. Performance in subjects

Please tick a box for each subject your child takes

	Failing	Below average	Average	Above Average	
Reading or English	☐	☐	☐	☐	☐
History or social studies	☐	☐	☐	☐	☐
Arithmetic or maths	☐	☐	☐	☐	☐
Science	☐	☐	☐	☐	☐
Other school subjects, eg computer courses, Do not include PE					
_____	☐	☐	☐	☐	☐
_____	☐	☐	☐	☐	☐
_____	☐	☐	☐	☐	☐

9. Does your child attend a special needs school? No ☐ Yes ☐ ☐

10. Does your child receive additional support in class or attend a special class?

No ☐ Yes ☐ ☐

If yes, please describe _____

11. Has your child repeated any grades?

No ☐ Yes ☐ ☐

If yes, please state grades and reasons _____

12. Has your child had any learning problems in school?

No ☐ Yes ☐ ☐

If Yes, please describe _____

When did these problems start? _____

Have these problems ended? No ☐ Yes ☐ ☐

☐

1 ☐ 2 ☐ 3 ☐ T ☐

D. Your Child's Behaviour

For each of the following items, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all the items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of your child's behaviour over the last six months.

	Not true	Somewhat true	Certainly true	Office Use
1. Considerate of other people's feelings	☐	☐	☐	☐
2. Restless, overactive, cannot stay still for	☐	☐	☐	☐
3. Often complains of headaches, stomach-aches or sickness	☐	☐	☐	☐
4. Shares readily with other children (treats, toys, pencils etc.)	☐	☐	☐	☐
5. Often has temper tantrums or hot tempers	☐	☐	☐	☐
6. Rather solitary, tends to play alone	☐	☐	☐	☐
7. Generally obedient, usually does what adults request	☐	☐	☐	☐
8. Many worries, often seems worried	☐	☐	☐	☐
9. Helpful if someone is hurt, upset or feeling	☐	☐	☐	☐
10. Constantly fidgeting or squirming	☐	☐	☐	☐
11. Has at least one good friend	☐	☐	☐	☐
12. Often fights with other children or bullies	☐	☐	☐	☐
13. Often unhappy, down-hearted or tearful	☐	☐	☐	☐
14. Generally liked by other children	☐	☐	☐	☐

	Not true	Somewhat	Certainly	*Office*
15. Easily distracted, concentration wanders	☐	☐	☐	☐
16. Nervous or clingy in new situations, easily looses confidence	☐	☐	☐	☐
17. Kind to younger children	☐	☐	☐	☐
18. Often lies or cheats	☐	☐	☐	☐
19. Picked on or bullied by other children	☐	☐	☐	☐
20. Often volunteers to help others (parents, teacher, other children)	☐	☐	☐	☐
21. Thinks things out before acting	☐	☐	☐	☐
22. Steals from home, school or elsewhere	☐	☐	☐	☐
23. Gets on better with adults than with other children	☐	☐	☐	☐
24. Many fears, easily scared	☐	☐	☐	☐
25. Sees tasks through to the end, good attention span	☐	☐	☐	☐

Office Use

P	_____	☐	H _____	☐
			E _____	☐
			C _____	☐
			F _____	☐
			T	☐

26. Overall, do you think that your child has difficulties in one or more of the following

No ☐
Yes, minor difficulties ☐
Yes, definite difficulties ☐
Yes, severe difficulties ☐ ☐

If 'No', please complete the questions on the next page.
If you have answered "Yes", please answer the following questions about these difficulties:

27. How long have these difficulties been present?

Less than a month ☐
1-5 months ☐
6-12 months ☐
Over a year ☐

28. Do the difficulties upset or distress your child?

Not at all ☐
Only a little ☐
Quite a lot ☐
A great deal ☐ ☐

29. Do the difficulties interfere with your child's everyday life in the following areas?

	Not at all	Only a little	Quite a lot	A great deal	
Home life	☐	☐	☐	☐	☐
Friendships	☐	☐	☐	☐	☐
Classroom/ Learning	☐	☐	☐	☐	☐
Leisure activities	☐	☐	☐	☐	☐

30. Do these difficulties put a burden on you or the family as a whole?

Not at all ☐
Only a little ☐
Quite a lot ☐
A great deal ☐ ☐

31. Does your child need supervision more than half of the time?

Yes ☐ No ☐

E. What is Your Child's Ethnic Group

Choose ONE section from A to E, then tick the appropriate box to indicate your child's cultural background.

A. White

British ☐ Irish ☐

Any other White background _____

B. Mixed

White and Black Caribbean ☐

White and Black African ☐

White and Asian ☐

Any other Mixed background: _____

C. Asian or Asian British

Indian ☐

Pakistani ☐

Bangladeshi ☐

Any other Asian background: _____

D. Black or Black British

Caribbean ☐

African ☐

Any other Black background: _____

E. Chinese or other ethnic group

Chinese ☐

Any Other: _____

* census 2001 ☐

If you have any other concerns about your child, please tell us about them here.

_____

_____

_____

_____

_____

Please tell us the three best things about your child.

1 _____

2 _____

3 _____

Please complete the following

This form was completed by:

Name: _____

Signature: _____ Date | | | |

Thank you for your time and help in the completion of this questionnaire

9.7 Appendix G: Ethical approval

NHS

Direct Dial 298004/298013

SJE/JEC

- 8 APR 2002

4 April 2002

Private and Confidential

North Staffordshire Health

Research Ethics Committee
Heron House
Great Fenton Business Park
Grove Road
Stoke on Trent
ST4 4LX

Professor N. Marlow
Professor of Neonatal Medicine
Faculty of Medicine and Health Sciences
School of Human Development
Academic Division of Child Health
Floor E, East Block
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Nottingham NG7 2UH

Direct Dial: (01782) 298013
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Fax Number: (01782) 298298
Email: Janet.Clarke@nsha.wmids.nhs.uk
Web site: www.nsha.co.uk

Dear Professor Marlow

Project 1389
Long term outcome following treatment of bronchiolitis with continuous negative pressure (CNEP)
Project 1390
Assessment of functional health status, respiratory, behaviour and cognitive outcome at school age for children entered into a randomised trial of continuous negative extrathoracic pressure (CNEP) for respiratory distress syndrome

Thank you for your e-mail and enclosed revised parents first approach letters. These were noted and your projects had final approval at the recent meeting of the North Staffordshire Local Research Ethics Committee on the 27 March 2002. The Committee asked that the parents had only one more contact letter after the first one as any further contact could be classed as harassment.

We require an annual report on the progress of the study and a final report within three months of the completion of the study. If the study is terminated prematurely a report is required within fifteen days, indicating the reason for early termination. We also require a report of any unusual or unexpected results which raise questions about the safety of the research. Failure to produce such reports without acceptable reasons may result in suspension of the Committee's approval, in which case the research must cease.

The Committee requires to be informed of any proposed alterations to the protocol and any adverse events.

You will no doubt realise that whilst the Local Research Ethics Committee has given approval for the study on ethical grounds, it is still necessary for you to obtain management approval from the relevant Clinical Director and the costs and detail of the trial still have to be agreed with the Trust's Research and Development Group.

Approval lasts for three years unless the Committee explicitly states otherwise.

Research projects performed in North Staffordshire are subject to random independent audit.

Yours sincerely

J. E Clarke

Dr. S.J. Ellis
Chair
Local Research Ethics Committee

cc Dr. W. Lenney, Consultant Paediatrician, Paediatric Directorate, City General Hospital
R&D Office, c/o Pharmacy Department, City General Hospital

Queen's Medical Centre Nottingham NHS
University Hospital NHS Trust

Please ask for:
Linda Ellis, Administrative Assistant
Ext 41049. E-mail: linda.ellis@mail.qmcuh-tr.trent.nhs.uk

Trust Headquarters
Research and Development
Queen's Medical Centre
University Hospital NHS Trust
Nottingham
NG7 2UH

Tel: 0115 970 9049
Fax: 0115 8493295

Our Reference: **CS070102**

7th June 2002

Professor N Marlow
Academic Division of Child Health
D Floor
East Block
UHN

Dear Professor Marlow

Re: **Long Term Outcome Following Treatment Of Bronchiolitis With Continuous Negative Extrathoracic Pressure (CNEP)**

The Ethics Committee met on 3rd September 2001 and approved the project subject to your providing of some information, or clarification. We are now in receipt of this, and the project is now fully approved, including the protocolfinal vesion dated 18.7.01, parent information sheet version 1.2 – Sunday 28th April 2002 and parent consent form.

The Ethics Committee requires that:

i) Serious adverse reaction/events, which occur during the course of the project, are reported to the Committee.

ii) Changes in the protocol are submitted as project amendments to the Committee.

iii) Yearly reports and a final report on the project to be submitted. (Forms will be sent to Lead Investigator for completion).

Kind regards

Yours sincerely

Dr M Hewitt
Honorary Secretary
Ethics Committee