ORAL PREDNISOLONE FOR PRESCHOOL CHILDREN WITH ACUTE VIRUS-INDUCED WHEEZING

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by

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To Sindhu, Gopika and my Parents

Abstract

Background

Attacks of wheezing induced by upper respiratory viral infections are common in preschool children between the ages of 10 months and 6 years. Systematic review assessing the efficacy of various medications in the management of viral wheeze in this age group found no evidence for routine use of inhaled corticosteroids. A short course of oral prednisolone is widely used to treat preschool children with wheezing who present to a hospital, but there is conflicting evidence regarding its efficacy in this age group.

Methods

We conducted a randomised, double-blind, placebo-controlled trial comparing a 5 day course of oral prednisolone (10mg once a day for children 10 to 24 months of age and 20 mg once a day for older children) with placebo in 700 children between the ages of 10 months and 60 months. The children presented to three hospitals in England with an attack of wheezing associated with a viral infection; 687 children were included in the intention-to-treat analysis (343 in the prednisolone group and 344 in the placebo group). The primary outcome was the duration of hospitalisation. Secondary outcomes were the score on the Preschool Respiratory Assessment Measure, salbutamol use, and a 7-day symptom score.

Results

There was no significant difference in the duration of hospitalisation between the placebo group and the prednisolone group (13.9 hours vs. 11.0 hours; ratio of geometric means, 0.90; 95% confidence interval, 0.77 to 1.05) or in the interval between hospital admission and signoff for discharge by a physician. In addition, there was no significant difference between the two study groups for any of the secondary outcomes or for the number of adverse events.

Conclusion

In preschool children presenting to a hospital with mild-to-moderate wheezing associated with a viral infection, treatment with oral prednisolone was not superior to placebo. Our results suggest that oral prednisolone should not be routinely given to preschool children presenting to the hospital with acute, mild-to-moderate virus-induced wheezing.

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Abbreviations

BDP..... Beclomethasone dipropionate

BTS..... British Thoracic Society

CI..... Confidence Interval

COREC..... Centre of Research Ethical Campaign

CTA..... Clinical Trial authorisation

CV..... Curriculum Vitae

DB..... Double Blind

eNO..... Exhaled nitric oxide

EVW……....Episodic viral wheeze

FP.....Fluticasone Propionate

GCP..... Good Clinical Practise

GINA.....Global Initiative for Asthma

GP..... General Practitioner

LRA..... Leukotriene receptor antagonists

LREC..... Local Research Ethics Committee

LRI..... Leicester Royal Infirmary

LRTI .....Lower respiratory tract infection

mg .....Milli gram

MHRA..... Medicines and Healthcare Products Regulatory Agency

MREC..... Multicentre Research Ethics Committee

MTW……..…..Multiple trigger wheeze

NA.....Not Applicable

PAS..... Patient Administration System

PD……..Pharmacodynamics

PK…….Pharmacokinetics

PRAM..... Preschool Respiratory Assessment Measure

PVW..... Preschool viral wheeze

QMC..... Queens Medical Centre

RCPCH..... Royal College of Paediatrics and Child Health

RDBPC.....Randomised Double Blind Placebo Controlled

RMCH……Royal Manchester Children's Hospital

RSV.....Respiratory syncytial viruses

RTBPC.....Randomised Triple Blind Placebo Controlled

SD.....Standard Deviation

TWICS .....Treatment for Wheeze In Children With Cortico Steroids

UK..... United Kingdom

URTI..... Upper respiratory tract infection

Declaration

I applied for ethical & MHRA approval for the trial. I designed all data entry forms and created the database in Microsoft Access for data entry. I recruited 550 of the 700 children to the trial and collected data on 575 children. I was responsible for the day to day conduct of the trial. This involved training doctors to recruit children for the trial, data recording on the data sheet, regularly updating nursing staff and doctors on the progress of the trial, organising steering group meeting. I inputted the whole data of the trial on to the database and along with Paul Lambert (Statistician) analysed the data.

I underwent GCP training and gained valuable experience in using Access, excel and SPSS. I also gained experience in Ethical & MHRA application process.

I presented the results of the trial in RCPCH plenary session and various other regional, national and international meetings.

PART 1

Chapter 1: Introduction

There is now a consensus that the clinical label of "asthma" encompasses different phenotypes of wheeze, each associated with a different cluster of risk factors[1-4]. However it remains unclear whether these groups are associated with different patterns of pulmonary inflammation, and responses to therapy[5-9]. Since the inflammatory substrates and risk factors of atopic asthma are well defined, it serves as a point of reference for all asthma phenotypes. Atopic asthma is characterised by airways hyper reactivity, chronic symptoms with intermittent acute attacks, skewing of pulmonary T cells to a Th2 phenotype, increased total and aeroallergen specific IgE, and increased airway eosinophils[10, 11]. Atopic asthma predominates in school-age children with physician diagnosed asthma[12]. By contrast, the clinical picture of asthma in the majority of preschool children (between 1 and 5 yrs) is characterised by transient episodes (attacks) of wheeze trigged by viral-colds, with few or no interval symptoms such as activity-induced cough and wheeze [13-17]: a pattern of asthma labelled as "Preschool viral-wheeze" (PVW)[18, 19].

1.1: Epidemiology of Viral wheeze

Most of the evidence suggesting that PVW with out interval symptoms may be a distinct phenotype of asthma comes from epidemiological studies. For example, Cogswell and colleagues[20, 21] prospectively followed a cohort of babies (n=67) at increased risk of developing atopic disorders over a 11 year period, and demonstrated that wheeze in the first two years of life is not a risk factor for atopic asthma in later childhood. In Tucson USA, Martinez et al. [22] studied over 800 children from birth, and identified three distinct wheezing pattern at 6 years of age: i) transient wheeze (the majority)- children who had at least one episode of viral wheeze during the first 3 years of life but no wheezing at 6 years of age, ii) late onset wheeze – children with no viral-wheeze during the first 3 years of life but had developed wheeze at 6 years of age, and c) persistent wheeze (the minority); children with at least one episode of viral- wheeze during the first 3 years of life and who continued to wheeze

at 6 years of age. Transient wheeze was not associated with any of early markers of atopy. By contrast, persistent wheeze had associated risk factors that were characteristic of classical, atopic asthma (elevated cord blood IgE and maternal history of asthma).

In the Isle of Wight study, Kurukulaaratchy and colleagues [7] evaluated the natural history of asthma and allergic disorders on a whole population birth cohort, established in 1989. They reported that, compared to transient wheezers, persistent wheezers showed significantly more physician-diagnosed asthma in early life ($p<0.005$ at 2 years), experienced greater multiple hospital admissions ($p=0.024$), specialist referral ($p=0.009$), use of inhaled ($p<0.001$) and oral steroids ($p<0.001$). By 10 years of age persistent wheezers had significantly impaired baseline lung function and enhanced bronchial hyper-responsiveness compared with non-wheezers.

Recently, Caudri et al.[23, 24] reported on a Duth birth cohort of 3963 children and showed that only 14% (178 of 1230) children with parent reported pre school wheeze had a diagnosis of asthma at 8 years of age.

In summary these epidemiological studies strongly suggest that the majority of children with PVW do not have atopic asthma and justifies calling PVW a separate phenotype of asthma.

Classification of wheeze based on epidemiological studies may not be beneficial in a clinical setting. To aid the clinicians, European Respiratory Society in 2008 produced an evidence based document for the management of wheezing in children, where 2 phenotypic groups were defined - 1. Episodic viral wheeze and 2. Multiple trigger wheeze [55].

In Episodic viral wheeze (EVW) children are well between the episodes of wheeze and wheezy episodes are preceded by viral upper respiratory tract infection. EVW are commoner in pre school children. Generally children grow out of EVW by 6 years of age.

In Multiple trigger wheeze (MTW) children wheeze with triggers other than viral infection. Unlike EVW, MTW is seen in children of all age group.

Aetiology of both Episodic viral wheeze and Multiple trigger wheeze are not well understood. Differences between Episodic and Multiple trigger wheeze are summarised below.

	Episodic Viral wheeze	Multiple trigger wheeze
Definition	Episodes of wheeze triggered by viral URTI	Wheeze triggered by viral URTI and other factors.
Triggers	Viral URTI	Viral URTI and other triggers like tobacco smoke, allergen exposure, exercise
Interval symptom	Absent	Present
Age group	Most common in pre school age group	Present in all age group
Natural progress	Grows out by 6 year of age	Variable

In this thesis PVW is defined as Episodic viral wheeze.

1.2: Respiratory viruses causing PVW

All common respiratory viruses including respiratory syncytial viruses (RSV), rhinovirus, coronavirus, human metapneumovirus, parainfluenza virus and adenovirus can cause viral

wheeze [25]. Lemanske et al.[26] in a prospective study on 285 children from birth to 3 years found that first year wheezing caused by rhinovirus infection was the strongest predictor for the development of PVW. Martinez and colleagues[27] have studied the relationship between RSV lower respiratory tract infection (LRTI) in early child hood and subsequent wheezing and showed that RSV LRTI was an independent risk factor for wheezing up to 11 years of age. But this association was not seen at 13 years. Approximately half of the infants with RSV LRTI go on to develop recurrent wheezing in childhood [28-30].

1.3: Factors determining frequency & severity of wheeze

The majority of Preschool children with virus-triggered wheezing present with mild symptoms. However in a small group of children this can progress to severe wheezy attack needing treatment with intravenous bronchodilators, steroids and ventilatory support.

Various studies have looked at the factors determining the frequency and severity of episodes of viral wheeze[25, 31, 32] in children. Horn et al.[33] has shown prematurity and severity of first episode of wheeze to be a significant risk factor for subsequent wheezing episodes. Maternal cigarette smoking in utero[34], parental smoking[35], more than one sibling at home[36], and atopy [31, 32] have all been shown to lead to wheezing in childhood. Similarly, illness severity, viral aetiology and allergic sensitisation have all been shown to lead to recurrent wheezing [37-40].

1.4: Diagnosis of PVW

PVW is diagnosed based on clinical history. The majority of children with PVW present with a history of wheeze preceded by symptoms consistent with an upper respiratory tract infection. Microbiological confirmation of upper respiratory tract infection is not helpful in the management of PVW [41]. Chest X-Ray, though helpful in excluding acute collapse or consolidation of the lung adds very little towards treatment of PVW.

Lung function tests are of limited value in treating PVW. Forced expiratory flow, though, reduced in children with viral wheeze [42-45], is not helpful in differentiating PVW from recurrent wheeze. However lung function tests are useful in establishing a diagnosis of reversible airways disease and excluding restrictive disorders and vocal cord disorders [46, 47]. Exhaled nitric oxide (eNO), an indicator of airway inflammation [48], is raised in children with atopic wheeze [49]. eNO level which is raised during an acute asthma exacerbation [50], may return to normal when treated with corticosteroids [51, 52]. The value of eNO measurements in the management of PVW is limited due to 1. Difficulty in performing eNO measurements in young children and 2. Lack of reference values for children less than 4 years[53].

1.5: Economic impact of PVW

1.5.1: Prevalence of PVW

Attacks of wheezing that are induced by viral infections of the upper respiratory tract are common in children under age of 6 years [21, 54]. In the first three years of life one in three children would have suffered from at least one episode of wheeze [55]. The incidence of wheezing in preschool children is three times that of school age children [56, 57]. However majority of pre school children who wheeze with cold become symptom free by 6 years of age [58-60].

Prevalence of wheeze, in children, has increased substantially in the last decades [61-63]. Kuehni et al.[14] conducted population surveys, by parent completed postal questionnaire, in 1990 and 1998, and showed an increase in prevalence of wheeze. Significant increase in prevalence was noted in reported wheeze ever, current wheeze, diagnosis of asthma, treatment for wheeze, and admission for wheeze or other chest trouble. Prevalence when analysed based on wheezing patterns showed an increase both in children with viral wheeze and in those with the classic asthma pattern of wheezing with multiple triggers. The authors concluded that over reporting of mild (infrequent) symptoms or diagnostic transfer could not explain the increase

in prevalence. A systematic review of worldwide variations of the prevalence of wheezing symptoms in children, reported United Kingdom (UK) to have the highest prevalence of wheeze among all countries from where data is available[64].

1.5.2: Costs of PVW

Although estimation of the costs of providing care for patients with a particular disease can be imperfect, it provides insight into the extent of the problem. Due to the high prevalence of the condition, viral wheeze has a significant financial impact on the health care systems. This involves direct cost accounted by GP and hospital visits and indirect costs due to parental time off work to provide child care. Stevens et al.[65] in 1999, estimated that 1-5 year old children with wheeze in UK cost £53 million, accounting for 0.15% of the total budget of the UK National Health Service. The greatest expenditure, £34 million, was for primary care representing 65% of the total health care costs. Furthermore, they estimated the costs to society of caring for preschool children who attended hospital for viral-wheeze to be £2.6 million[66].

Chapter 2: Treatment of PVW

2.1: Review of Literature

British Thoracic Society (BTS) guidelines[67] stratify treatment of childhood asthma by age. PVW is not categorised as a separate entity because very few trials have considered the phenotype mix of preschool asthma. Hence a systematic review was conducted to examine the current evidence for the treatment of PVW, specifically whether treatment with inhaled oral and topical steroids, bronchodilators and leukotriene receptor antagonists reduces the frequency of attacks, and their severity.

2.1.1: Aim

To assess the current evidence in the use of 1. Inhaled steroids 2. Oral steroids 3.Topical nasal steroids 4. Bronchodilators and 5. Leukotriene receptor antagonists for the management of PVW.

2.1.2: Search strategy

For this review, PubMed, Cochrane databases were searched for randomised double-blind placebo controlled clinical trials of inhaled corticosteroids, oral corticosteroids, topical nasal steroids, bronchodilators and leukotriene receptor antagonists for preschool asthma. Search terms used were 'viral wheeze or asthma' and 'corticosteroids', 'inhaled corticosteroids', 'topical nasal steroids', 'bronchodilators', 'leukotriene receptor antagonists' and 'montelukast'(Table 1). It was assumed that trials that recruited children with recurrent attacks of wheeze between 6 months and 6 years were treating PVW, since studies have shown that respiratory viruses are present in the upper airway of 85% of children presenting to hospital with acute wheeze. A cut off of 6 months was used since in younger children, it is difficult to separate PVW from RSV bronchiolitis. Trials in preschool children with persistent interval symptoms of asthma i.e., symptoms on three or more days per week, were considered

to have recruited a more heterogeneous mix of phenotypes, and therefore classified as of less relevance to PVW.

2.1.3: Current evidence

Inhaled steroids

There is no doubt that inhaled corticosteroids are beneficial for preventing daily symptoms in adults with classical atopic asthma[68, 69]. Five clinical trials were identified which were relevant to PVW. One addressed the efficacy of prophylactic inhaled corticosteroids, and four addressed episodic high dose inhaled corticosteroids (Table 2).

Wilson and colleagues [70] in a randomised double blind parallel trial on 41 children aged 8 months to 6 years with episodic PVW, (defined clinically as wheezing episodes associated with clinical viral infection, with no or minimal symptoms between the episodes) compared the effect of four months daily treatment of budesonide 400 μg per day with placebo and found no difference in mean daily symptom score, mean score per episode and symptoms between the episodes between two groups, suggesting no benefit for regular maintenance therapy.

In contrast, Connett and colleagues [71] studied the efficacy of intermittent budesonide or placebo in 25 children with a previous history of PVW. Inhaled steroid treatment was started at the onset of an upper respiratory tract infection and continued for 7 days or until symptoms had resolved. Children who received budesonide had significantly lower mean day and night time wheeze in the first week after infection. The researchers concluded that intermittent inhalation of budesonide can modify the severity of pre school viral wheeze to a "modest extent".

Svedmyr et al. [72] studied 55 children aged 1- 3 years with a previous history of PVW (defined as at least three episodes of wheezing during upper respiratory tract infection (URTI) with no or minimal symptoms between the episodes) for the effect of 10 day course of budesonide (400 μg four times per day for 3 days and twice a day for a further 7 days) started at the first sign of URTI. Symptom scores were lower in children treated with budesonide than with placebo, but the beneficial effect was more pronounced for the less clinically significant symptoms of "cough" and "noisy breathing". There was no effect of budesonide on hospitalisation rate.

Wilson et al.[73] compared high dose beclomethasone dipropionate (BDP) (750 μg three time per day for 5 days), with placebo in 24 pre school children who had experienced at least two episodes of acute wheeze in the preceding three months, and found both day and night time symptoms over the first week of attack were significantly reduced in children receiving BDP.

In a triple blinded, parallel-group, randomised, placebo-controlled trial, Francine Ducharme and colleagues [74] studied the use of high dose fluticasone for moderate to severe viral induced wheezing in children. 129 children, aged 1-6 years, were given either 750 μg of fluticasone propionate (FP) or placebo twice daily for a maximum of 10 days at the onset of upper respiratory tract infection. During the study period of 12 months, pre-emptive treatment with high dose fluticasone as compared with placebo reduced the use of rescue oral corticosteroids (8% vs. 18%, odds ratio - 0.49, 95% confidence interval (CI) - 0.30-0.83), fewer visits to hospital involving two or more salbutamol treatment (26% vs. 42%, p=0.03), shorter duration of symptoms (odds ratio - 0.85, 95% CI - 0.73-0.99), smaller use of beta –2 – agonists (odds ratio - 0.85, 95% CI - 0.72-1.00) and smaller negative effects on parents life. Even though there was no significant difference between the two groups in basal cortisol levels, bone mineral density and adverse events, treatment with fluticasone was associated with smaller gain in height and weight. Authors advised against this management approach in PVW, due to

the potential for its overuse, until the long term effects on growth are studied in longer clinical trials.

Taken together, these data suggest that modest improvement in symptoms may be achieved using episodic, relatively high dose inhaled corticosteroids, but that regular inhaled steroids at normal doses, have little impact on attacks.

Oral steroids

In older children a short course of systemic steroids both facilitates recovery from acute attacks and prevents further asthma exacerbations after discharge from hospital[75, 76]. By contrast, the effect of oral steroids in PVW is unclear. In a randomised, double blind, placebo-controlled trial of 230 children aged 6 months to 35 months, Csonka et al.[77] (Table 3) investigated the efficacy of short course of oral prednisolone in PVW (acute tachypnoea, wheezing, or use of accessory muscles in the presence of an apparent viral upper respiratory tract infection). Children with a previous diagnosis of asthma or two or more previous wheezing episodes were excluded. Each child received either oral prednisolone 2 mg/kg/day or oral placebo for 3 days from the time of presentation to the paediatric emergency department with viral wheeze. The primary outcome was development of "severe respiratory symptoms requiring the use of additional asthma medication". Even though there was no difference in the hospitalisation rates between two treatment groups (53 and 54%), there was less need for "additional" asthma medication in the prednisolone-treated hospitalised children (18 vs. 37%), which was associated with a reduced length of stay (2 days vs. 3 days). However complications in prednisolone-treated children who were not admitted to the hospital wards were not recorded. The trial was adequately powered for its primary outcome, and does therefore provide the first clear evidence that systemic steroids may influence PVW severity.

Set against these data, two trials addressing the role of prednisone in an outpatient or home setting have shown no benefit (Table 2). In a randomised double-blind placebo controlled trial, Grigg and collegues[78] studied the effect of a short course of parent initiated oral prednisolone for PVW in children aged 1-5 years, who has previously been hospitalised with PVW. To ensure that a potentially responsive subgroup with "atopic" risk factors, were not missed, children were stratified by systemic eosinophil priming status. The study did not show any difference in any of the primary symptom outcome measures (7 days mean day and night time symptom scores) in 153 children who subsequently developed a further episode of PVW. Furthermore, there was no difference in the number of salbutamol actuations per day, and no evidence for parental preference for prednisolone. As with all (community based) studies it is possible that parents were not compliant with the trial therapy. However these results are similar to that of Webb et al.[79] who prescribed placebo or prednisolone (2 mg/kg body weight per day for 5 days) in an outpatient setting to 38 children aged less than 18 months with "wheezy bronchitis"-a term probably synonymous with PVW. In this cross over study, prednisolone did not reduce daily symptom scores of cough, wheeze, and breathlessness and secondary outcome analysis found no evidence of a beneficial effect within subgroups of children aged less than 6 months, 6-12 months and 12-18 months.

In summary, there is paucity of evidence for the routine use of intermittent oral steroids in PVW. The trial of Csonka shows promise, but needs replicating before the results can be generalised to a European population. The lack of studies is remarkable for such a prevalent condition.

Topical nasal steroids

The mechanism for PVW remains unclear. There has been speculation that there is "cross talk" in that inflammation in the nose triggers inflammation in the lung[80]. To address this putative mechanism, Silverman and colleagues,[19] performed a double blind, randomised

controlled trial of prophylactic nasal corticosteroids (one dose of fluticasone aqueous nasal spray into each nostril twice daily vs. placebo) in 50 children aged 12-54 months with a history of at least three episodes of PVW over the previous winter. The results showed no significant difference in the severity of nocturnal symptoms, in daytime symptoms, activity or total scores during episodes between the two groups, and provides no indication that nasal corticosteroid treatment can prevent PVW.

Bronchodilators

Although short acting bronchodilators are widely used to treat PVW, there are few trials assessing their efficacy. Cochrane reviews have not looked specifically at the effect of bronchodilator therapy in PVW, but have assessed their efficacy in wheezy children above and below 2 years of age. This age classification means that it is difficult to separate the effects of bronchiolitis and atopic asthma in the younger age group. It is however reasonable to assume in reviews including children < 2yrs, a significant proportion of children may have PVW. The efficacy of inhaled short acting beta agonists for "recurrent wheeze" (defined as two or more previous episodes of wheeze, not related to another form of chronic lung disease) in children less than two years of age was reviewed by Chavasse et al.[81] Eight randomised controlled trials comparing the effect of beta 2-agonists versus placebo in children under two years of age who had two or more previous episodes of wheeze were identified. Three trials had studied at children <14 months of age, while 5 recruited children between 2 months to 25 months. These data were markedly heterogeneous, a fact that severely limited the performance of between study comparisons. However, it was concluded that there is "no clear benefit of using beta 2-agonists in the management of recurrent wheeze in the first two years of life", with a caveat that "there is conflicting evidence". To date there are no clinical trials looking at the effect of short acting beta 2-agonists for PVW in children aged 2-6 years.

A further Cochrane review examined the effectiveness of inhaled anti-cholinergic therapy (e.g. ipratropium bromide) [82] for acute wheeze in children under 2 yrs of age. Randomised trials that compared anti-cholinergic therapy with placebo or beta-2 agonists in wheezing children <2yrs were identified, and those that recruited children with acute bronchiolitis and chronic lung disease were excluded. No clear benefits in outcomes such as duration of hospitalisation or improvement in oxygenation were found. However, there was significant improvement in clinical scores at 24 hours when children were given combination of ipratropium bromide and beta-2 agonist compared to placebo. The authors concluded that there is "not enough evidence to support the uncritical use of anti-cholinergic therapy for wheezing infants". It is of interest that in the >2yr age range, in whom the effectiveness of anticholinergics is assumed, only eight of the hundreds of papers examined met the inclusion criteria of the Cochrane process[83]. Three papers compared the effects of anticholinergic drugs in wheezing children with placebo, and a meta-analysis of these results demonstrated no statistically significant benefit for the use of anticholinergic drugs over placebo in any of the outcome measures.

In summary, there are very little data to justify the use of inhaled bronchodilators in acute PVW. However it is our clinical impression that some children do respond to nebulised salbutamol and the systematic review may have overlooked responsive subgroups. Our current recommendation is to assess responsiveness individually using objective markers if possible. There are no studies looking at the effect of long acting bronchodilators on PVW.

Leukotriene receptor antagonists

Cysteinyl leucotriene receptor antagonist, montelukast, provide protection against bronchoconstriction and improves airway responsiveness[84, 85]. Studies in pre school children with persistent symptoms (i.e., not meeting the criteria for PVW) defined as three or more episodes of asthma symptoms in a year and needing beta agonists for 8 days during a 2 week

placebo base line period, montelukast has been shown to produce significant improvement compared with placebo in multiple parameters of asthma control including day and night time asthma symptoms, the percentage of days with asthma symptoms (59% vs. 64%), percentage of days with out asthma (34% vs. 28%), the need for beta-agonist (49% vs. 55%), or oral corticosteroids (19% vs. 28%)[86]. For young children, an useful feature of montelukast is that it is potentially anti-inflammatory,[87] and is not associated with steroid side effects. In 2-8 year olds, Szefler et al.[88] found that nebulised budesonide was more effective than montelukast in reducing exacerbations of wheeze.

Bisgaard et al.[89] in a multi centre, double blind parallel group study, investigated the effect of regular montelukast therapy on asthma exacerbations in children aged 2-5 years, with a history of "intermittent" asthma associated with common cold and minimal symptoms between the episodes. Children were randomised to receive either oral montelukast or placebo once a day for 12 months. During the study period montelukast significantly reduced the rate of asthma exacerbations (presumably PVW) by 32%, and the rate of inhaled corticosteroid use and beta agonist usage by 30% and 40% respectively. The authors concluded that exacerbations of mild intermittent asthma can be successfully treated with montelukast. Robertson et al.[90] compared the effect of intermittent montelukast, started when patients developed signs of cold, with placebo in 220 children with episodic wheeze and showed a 30% reduction in unscheduled health visits. However there was no difference in hospitalisations, duration of episodes, beta agonist or prednisolone use between two groups. These data on montelukast are promising but need replication in a large independent trial.

Other treatments

There is no evidence for the use of chromones in PVW [91]. Whereas sodium cromoglycate is shown to be of some benefit in adult asthmatics the evidence in asthmatic children is contentious and is under review. Similarly nedocromil sodium is of some benefit in children

aged 5-12 years and children aged more than 12 years. Tasche et al.[92] studied 218 children aged 1-4 years with moderate asthma and concluded that cromolyn is not more effective than placebo.

Xanthines are effective in the treatment of asthma, but its effect in pre school viral wheeze was insignificant [93]. Effect of antihistamines in the management of Pre school wheeze was analysed in a cochrane review [94]. Compared to placebo ketotifen was able to reduce the bronchodilator treatment. However the participant description in the studies were not clear enough to differentiate them into episodic viral wheeze or chronic asthma.

2.1.4: Limitations of the review

This review is limited by considering only one part of the asthma spectrum. The review has assumed PVW as a separate phenotype, but this term still might not be true. For instance do Pre School children who wheeze with URTI and with out URTI differ from children who wheeze only with viral URTI ? It might be possible to further refine phenotypes of pre school asthma using markers of inflammation (eg eNO), but to date few trials have been stratified by patterns of inflammation in the preschool age group.

2.1.5: Summary of current evidence

To date there is no evidence for the routine use of inhaled corticosteroids in PVW. Further clinical trials are needed to assess the efficacy of oral corticosteroids but use of high dose intermittent steroids show the most promise. Regular montelukast shows some promise but the data are not definitive. There are no clinical trials specifically assessing the use of theophylline and chromones in PVW.

2.2: Pharmacokinetics & Pharmacodynamics of corticosteroids

Safety and efficacy profile of an inhaled corticosteroid is influenced by the Pharmacokinetic (PK) properties and the associated pharmacodynamic (PD) effects of the drug. PK & PD properties of corticosteroids such as small particle size, high gluco corticoid receptor binding affinity, long pulmonary residence time and lipid conjugation determines the efficacy of the drug by increasing or prolonging the anti-inflammatory effects of the drug. Safety of the drug is determined by PK properties like on-site activation in the lung, low oropharyngeal exposure, negligible bioavailability, high protein binding and rapid systemic clearance. Corticosteroids are effective in the treatment of asthma because of their ability to interfere in the multiple pathways in the inflammatory process. It reduces airway inflammation and hyper responsiveness by altering the production of mediators of inflammation such as macrophages, eosinophils, lymphocytes and mast cells. Currently available inhaled corticosteroids have different PD and PK properties.

2.3: Side effects of corticosteroids and bronchodilators

Inhaled steroids can cause various local and systemic side effects. Local side effects commonly encountered are hoarseness, reflux cough, broncho spasm, pharyngitis and candidiasis. The occurrence of the side effects is dependent on the type and dose of inhaled corticosteroid.

Systemic side effects which are of more clinical significance include effect on growth and adrenal suppression. It can also cause thinning of skin, glaucoma and osteoporosis. Exogenous corticosteroids can suppress Hypothalamic–pituitary-adrenal axis and lead to adrenal suppression. The severity of adrenal suppression is dependent on the type and dose of corticosteroids.

Bronchodilators are usually well tolerated. Side effects like tremor, headache, palpitations, agitations and hypo kalemia are seen at higher dosage.

2.4: Current practice

2.4.1: Introduction

Despite the huge prevalence of pre school viral wheeze, there is no consensus among clinicians in the management of PVW. A Questionnaire survey was conducted among general and respiratory paediatric consultants in Trent region to assess their understanding of term PVW and treatment of the condition.

The objective of this survey was:

1. To ascertain whether clinicians differentiated between children who wheeze exclusively with viral infection with no interval symptoms from children who wheeze with viral illness and with other triggers e.g.: exercise, allergens etc.
2. To assess acute and outpatient management of PVW.

2.4.2: Methods

Ten General Paediatricians who participated in acute on call rota were asked what they would like to know about the management of PVW. Based on the information gathered a questionnaire was devised. This was then reviewed by ten other paediatricians who participated in acute rota. They were asked to make changes to the content and style of the questions as they felt needed. After making the changes, a pilot survey was conducted among 10 Paediatricians. All 10 Paediatricians returned the survey and their suggestions were incorporated before the final questionnaire was drafted.

Anonymous questionnaire (Appendix 2) was send to 100-consultant paediatricians in the Trent region. Responses from consultants participating in acute general or respiratory

paediatrics were analysed. They were asked whether they differentiated between children who wheeze exclusively with viral infection with no interval symptoms (PVW) from children who wheezed with viral illness and with other triggers. To ascertain the acute management they were asked to indicate percentage of children started on oral steroids, dose and duration of steroids, first choice bronchodilator with mode of delivery and leukotriene receptor antagonist usage. For long-term (outpatient) management of children with wheeze they were asked what percentage of children was started with inhaled steroids and leukotriene receptor antagonists (LRA). For clinicians who differentiated between the two conditions, information on the management of both conditions was collected.

2.4.3: Results

Of the 100-questionnaire sent, 63 completed questionnaires were returned. 6 paediatricians did not participate in acute paediatrics and were not seeing children with viral wheeze. They were excluded from the final analysis. Of the remaining 57, 47 differentiated between PVW and wheeze with interval symptoms (Group 1) while 10 consultants managed them similarly (Group 2). Tables 3 & 4 show the management of an acute wheezy attack in group 1 & 2 respectively whereas Tables 5 & 6 show the outpatient management of wheeze.

In group 1 (Paediatricians who differentiated between PVW and wheeze with interval symptoms), for wheeze with interval symptoms, 88% of the consultants who responded used oral steroids in more than half of the children to manage an acute attack. In PVW this decreased to 48%. In group 2 (paediatricians who did not differentiate between PVW and wheeze with interval symptoms) this was 42% (3 out of 7). Majority of consultants in both groups did not use LRA in an acute situation. More than 90% of consultants in both groups used salbutamol as their first choice bronchodilator for an acute wheezy attack, while inhaler with spacer was preferred over nebuliser for delivery of medication (Tables 4 & 5).

When children with PVW were seen in an out patient settings, in group 1, majority of the paediatricians either did not use inhaled steroids (n=8, 21%) or used it in less than 25% of the children (n=22, 58%). For children with interval symptoms, preference reversed, with 14 consultants (49%) using it in more than 75% of the children. Similarly for PVW, majority of the paediatricians, (n=25, 57%) never advised their patients to use short course high dose inhaled steroids during an acute wheezy attack, where as for children with interval symptoms, trend reversed, with 64% (n=28) of the consultants advising their patients to use it always or some times during an acute wheezy attack. While 80% (n=36) of the paediatricians never used LRA for PVW, 58% (n=22) used it at least 25% of times for children with interval symptoms. In group 2, 87% (n=7) started inhaled steroids on at least 50% of their children, 90% (n=9) advised their patients to use high dose inhaled steroids always or some times during an acute wheezy attack and 50% never used LRA for treating wheeze in the outpatient clinics (Tables 6 & 7).

2.4.4: Discussion

PVW is one of the most common reason for hospital visit & admission in childhood. Despite the huge prevalence, clinicians varied widely in their management of PVW. This could partly be attributed to the lack of a national guideline in the management of PVW. Since this survey was conducted European Respiratory Society task force has produced an evidence based guideline in the definition, assessment and treatment of wheezing disorders in pre school children[55].

Most effective bronchodilators are short acting beta 2 agonists [95-99]. Despite the difference in opinions, majority of consultants preferred salbutamol over ipratropium bromide as their first choice bronchodilators. There is increasing evidence that inhalers with spacers are the most effective delivery system [100-102]. Systematic review by Cates et al.[100] showed that children who received beta 2 agonist through inhalers, compared to nebulisers, recovered quickly

during an acute wheezy attack. In this survey, most of the paediatricians preferred inhalers over nebulisers in the acute management of wheeze.

In the use of inhaled and oral steroids, management of PVW differed to that of wheeze with interval symptoms. Paediatricians preferred to use steroids for management of children with interval symptoms compared to PVW. Most consultants were reluctant to advise children on the use of high dose intermittent inhaled steroids in PVW. 87% of the responders used intermittent oral steroids for the acute management of PVW. This number was similar to the findings of a national survey conducted by Davies et al[23].

2.4.5: Limitations

This was a small survey conducted among 100 paediatricians. Only 63% of the paediatricians returned the questionnaire and further 6% were removed from final analysis as they did not participate in the acute on call rota making the sample size small. A formal statistical analysis of the data was not conducted limiting the strength of conclusions. However as majority of the doctors who returned the questionnaire (57/63) participated in the on call rota, the data was representative of the UK clinical practise.

2.4.6: Conclusions

In the management of wheeze in pre school children, paediatricians differentiated between PVW and wheeze with interval symptoms. Clinicians were reluctant to advise children, to use high dose intermittent steroids for PVW. Majority of paediatricians used intermittent oral steroids in managing an acute attack of PVW.

2.5: Oral corticosteroids for acute PVW

2.5.1: Background

Very few clinical trials have specifically targeted children with pre school viral wheeze. National guidelines, which are based on the efficacy of systemic corticosteroids in reducing the duration of hospitalisation in school-age children and adults with classic atopic asthma[76, 103, 104], recommend the use of oral corticosteroids for preschool children with virus-induced wheezing who present to a hospital[58, 67, 105]. However, the results of trials that have specifically addressed the questions of efficacy of systemic corticosteroids in young children with acute wheezing are contradictory[77, 106-108]. In a previous study, we found that a 5-day course of oral prednisolone that was initiated by parents at home at the first sign of an attack of wheezing did not significantly reduce parent-assessed symptom scores and the need for hospitalisation[78], whereas study by Csonka et al.[77] found a beneficial effect of prednisolone on severity and duration of symptoms. Thus, the role of oral corticosteroids for virus-induced wheezing remains controversial[109].

2.5.2: TWICS Trial

Surveys conducted nationally[23] and locally demonstrated lack of uniformity among clinicians in the use of oral corticosteroids in acute management of preschool viral wheeze. This was predominantly due to lack of good clinical trials. To address this clinical issue, we decided to conduct a large randomised double blind placebo controlled trial assessing the efficacy of a short course therapy with oral prednisolone in children presenting to hospital with virus-induced wheeze. Study was labelled as TWICS Trial –**T**reatment for **W**heeze **I**n Children **W**ith **C**ortico **S**teroids. We sought to ensure that at least one dose of oral prednisolone was administered by a health care professional and that a validated assessment of the severity of the child's symptoms was included.

2.5.2.1: Hypothesis and Outcome measures

We hypothesised that the outcome for preschool children (10 months to 5 years), admitted to the hospital with an attack of wheeze triggered by clinical viral infection (Preschool viral wheeze; PVW), and treated with oral steroids will be no different than for those children treated with placebo (null hypothesis).

The **primary** outcome measure was the duration of stay in hospital, since this has been used in therapeutic trials in paediatric respiratory medicine[110], and as an outcome measure in systematic reviews of systemic steroids in paediatric asthma [76]. Duration of hospitalisation, was divided into two time periods – the time from enrolment to the time of actual discharge from the hospital and the time form enrolment to the time that the patient was deemed to be "fit for discharge" (signoff for discharge)-since the time of actual discharge may be influenced by nonclinical factors.

The **secondary** (null) hypotheses were, then in comparison to placebo, treatment of children with PVW with oral prednisolone will **not**: 1. Reduce the severity of respiratory distress at 4, 12 and 24 hours. 2. Reduce the total severity of the attack, or the total amount of inhaled bronchodilators and 3. Reduce the re-admission to hospital within 4 weeks of discharge.

Secondary outcomes were the Pre School Respiratory Assessment Measure (PRAM) at 4, 12 and 24 hours (as assessed shortly after the administration of inhaled salbutamol) (Table 8); the total dose of inhaled salbutamol during hospitalisation (with 2.5 mg of the drug considered to be equivalent to10 actuations of a metered-dose inhaler); the mean 7- day symptom score, as assessed by a parent or guardian; the mean number of actuations of salbutamol given at home during a 7-day period; the time required for the child to be "back to normal"; and hospital readmission for wheezing within a month after discharge.

2.6: My role in the conduct of TWICS Trial

I (Researcher) was a grid trainee in Paediatric Respiratory Medicine at Leicester Royal Infirmary since March 2003. I was successfully interviewed for the post of research fellow for the TWICS trial in November 2004 and the post commenced in March 2005. Soon after my appointment in November, prior to my official start date as research fellow, I started the ethical approval application process for the trial. I completed the COREC application form and submitted all the necessary documents for the ethical approval to MREC on 18th January 2005. After few minor clarifications, approval for the Leicester Royal Infirmary site was granted on 18th February 2005. Following MREC approval, I submitted the MHRA application with the necessary documents on 1st of March 2005. MHRA approval was granted in April 2005. Immediately after obtaining the MREC and MHRA approval, I completed the forms and provided all the necessary documents to NOVA Laboratories to obtain the trial medications. I liaised with the trial pharmacists at LRI site to identify the most appropriate place to store the trial medications in accordance with the MHRA criteria. First set of trial medications were delivered to LRI in May 2005. Recruitment started at the LRI site in May 2005.

I designed all the data collection forms and created a Microsoft Access database for data entry. This was a time consuming process and needed many amendments. I started educating nursing staff, senior house officers and registrars about TWICS trial from April 2005. This involved purpose of the trial, eligibility criteria, data collection and how to contact me for recruitment. Every 6 months, I, identified a core group of 4 registrars and senior house officers who expressed interest in recruiting children for TWICS trial. These were either registrars who had a special interest in respiratory medicine or very keen and reliable senior house officers. This core group helped in my recruitment and data collection. I also ensured that they were GCP trained, to be eligible for recruiting children for the trial. For rest of the

junior doctors and nursing staff emphasis was made in identifying wheezy children who fulfilled the eligibility criteria and how to contact me for recruitment. Every 3 months, I updated the staff of the progress of the trial. This helped me enormously in my recruitment as once the staff realised that I am recruiting children actively into the trial, they also felt motivated in contacting me.

Usually when there is an increase in number of children with PVW attending the hospital, overall attendance in paediatric accident and emergency unit increases as well. Hence it was impossible to depend on on site doctors to recruit children for TWICS trial. When I am contacted for recruiting a child I completed the clarking and initial review of the child. I always made sure that the decision on the medication was made by another doctor. In a busy paediatric accident and emergency and admission unit this was a huge bonus as the children were seen quicker and freed up doctors to see other children there by reducing the waiting time in accident and emergency .

Once a child is recruited into the trial, I went back to review the child at 4, 12 and 24 hours to assess the PRAM score. If one of the core group doctors were on duty, and if they were available they completed the data sheet for me. Due to the seasonal nature of the trial, I was on site almost all days from September to February. I also collected the data on discharge, send the GP letter, made 1 week and 4 week telephone calls, filed all documents as per MREC requirements and entered the data on to the database.

LREC approval for Nottingham site was obtained in November 2005. Natasha Lafond, research nurse, coordinated the recruitment at Nottingham site. I trained Natasha on the conduct of the trail and visited Nottingham once every 6 months to educate doctors on the trial. I organised the steering group and data monitoring meetings, submitted the annual progress report of the trial to the trust and ASTHMA UK (Funding body).

I started my current post of Consultant Respiratory Paediatrician and Royal Manchester Children's Hospital on 1st of March 2007. By this time 650 children were recruited in to the trial. I had completed the data collection and data entry of 625 of these children before I left Leicester. Dr Priti Kenia coordinated the recruitment and data collection of the remaining 50 children and 700 th child was recruited in October 2007. I completed the data entry of 700 children in January 2008. Along with Dr Paul Lambert, the statistician for the TWICS trial, I decided on the statistical test to be used for analysing the data.

2.7: Timeline of TWICS trial

Appointed as Clinical Research Fellow for the TWICS trial	November 2004
Submission of the COREC application form to MREC	18th January 2005
MREC approval for the LRI site	18th February 2005
Start date of clinical research fellow job	1st March 2005
Submission of MHRA application	1st March 2005
MHRA approval for the study	April 2005
Designing of the data collection forms and access data base, initiation of staff training at LRI site & delivery of trial medication	April - May 2005
Recruitment of the first child at LRI site	May 2005
LREC approval for the Nottingham site	November 2005
Recruitment of the first child at Nottingham site	February 2006

Day to day conduct of the trial	May 2005 - February 2007
Last day as Clinical research fellow for the TWICS trial	28th February 2007
Started as Consultant Respiratory Paediatrician at RMCH	1st March 2008
End of Recruitment	October 2007
Completion of data entry and analysis of data	January 2008

Database searched	Pubmed
Limits	Human, Clinical trial, English, All children aged 0 -18.
Inhaled corticosteroids and viral wheeze	Number of hits: 14 Relevant studies: 3
Oral corticosteroids and viral wheeze	Number of hits: 8 Relevant studies: 4
Topical nasal steroids and viral wheeze	Number of hits: 1 Relevant studies: 1
Leukotriene receptor antagonist or montelukast and intermittent asthma	Number of hits: 380 Relevant studies: 1
Montelukast and intermittent asthma	Number of hits: 9 Relevant studies: 1
Bronchodilators and viral wheeze	Number of hits: 23 Relevant studies: 1

Database searched	Cochrane
Inhaled corticosteroids and viral wheeze	Number of hits: 4 Relevant studies: 1
Oral corticosteroids and viral wheeze	Number of hits: 2 Relevant studies: 0
Topical nasal steroids and viral wheeze	Number of hits: 0 Relevant studies: 0
Montelukast and intermittent asthma	Number of hits: 0 Relevant studies: 0
Bronchodilators and wheeze	Number of hits: 12 Relevant studies: 2

Table 1: Search Strategy

Study	Year & No	Selection criteria	Intervention	Outcome measures	Results
Wilson N et al.[70] RDBPC Parallel group study	1995, n=41	Age: 8m - 6 years Episodic viral wheeze	Budesonide (400μg/day) Vs Placebo for 4 months	Mean daily symptom score Mean score/ episodes Symptoms between episode	No difference No difference No difference
Wilson NM et al.[73] RDBPC Cross over study	1990, n=35	Age: 1-5 years Episodic asthma No trigger defined	BDP (750 μg/tds) Vs Placebo for 5 days	Symptom score Parental opinion	Significantly reduced in treatment (BDP) group Significantly more Parents felt BDP to be helpful.
Connett G et al.[71] RDBPC Cross over Study	1993, n=32	Age: 1-5 years Viral induced wheeze	Intermittent Budesonide (800 or 1600 μg/bd) Vs. Placebo	Symptom score Parental preference for inhaler	Mean day & night time wheeze significantly lower in treatment (Budesonide) group in the first week after infection Significantly increased preference for Budesonide
Svedmyr J et al.[72] RDBPC Parallel group study	1999, n= 55	Age: 1-3 years Asthma exacerbation No trigger defined	Budesonide Vs Placebo for 10 days	Symptom score	Significantly lower in children treated with Budesonide
Ducharme FM et al.[74] RTBPC Parallel group study	2009, n=129	Age: 1-6 years Viral induced wheeze	Fluticasone propionate (750 μg/bd) Vs. Placebo	Rescue steroids Hosp visits Duration of symptoms Gain in height & weight	Less in FP group Fewer visits in FP group Shorter in FP group Smaller gain in FP group

Table 2: Inhaled Corticosteroids in the management of PVW

RDBPC = Randomised double blind placebo controlled, FP = Fluticasone propionate

RTBPC = Randomised triple blind placebo controlled, BDP = Beclomethasone dipropionate.

Study	Year & No	Selection criteria	Intervention	Outcome measures	Results
Csonka et al.[77] RDBPC Trial	2003, n=230	Age: 6m–35months Viral wheeze	Oral Prednisolone Vs Placebo for 3 days	Development of severe respiratory symptoms requiring additional asthma medication Hospitalisation rate from emergency Dept Length of hospital stay Duration of symptoms	Significantly less in prednisolone group 18% vs. 37% (p=.018) No difference Shorter in prednisolone group 2 vs. 3 days (p=. 060) Significantly less in prednisolone group
Oommen et al.[78] RDBPC Trial	2003, n=217	Age: 1y - 5 years Viral wheeze.	Oral Prednisolone Vs Placebo for 5 days	Symptom score Mean salbutamol actuations per day Substitution of trial medication with prednisolone Parental preference Hospital admission	No difference No difference No difference No difference More in prednisolone group
Webb et al.[79] DB Partial cross over trial	1986, n=38	Age: 3m-17 months Viral wheeze.	Oral Prednisolone Vs Placebo for 5 days	Symptom score Parental preference	No difference No difference (No difference for the whole group or within sub groups 6-12m &12-18m)

Table 3: Oral Prednisolone in the acute management of PVW

RDBPC = Randomised double blind placebo controlled

DB = Double blind.

	PVW n (%)	Wheeze with interval symptoms
First choice Broncho dilators		
Salbutamol	42 (92)	45 (98)
Atrovent	2 (4)	0 (0)
Either	2 (4)	1 (2)
Choice of initial delivery device		
Inhaler with spacer	34 (77)	32 (70)
Nebulisers	6 (14)	7 (15)
Either	4 (9)	7 (15)
% of children with viral wheeze started on oral steroids		
None	4 (13)	0 (0)
1-25	5 (16)	1 (3)
26-50	7 (23)	3 (9)
51-75	5 (16)	4 (12)
76-100	10 (32)	26 (76)
% of children with viral wheeze started on LRA		
None	37 (90)	23 (66)
1-25	4 (10)	12 (34)
26-50	0 (0)	0 (0)
51-75	0 (0)	0 (0)
76-100	0 (0)	0 (0)

Table 4: Acute management of wheeze by paediatricians who differentiated between PVW and wheeze with interval symptoms (Group 1)

n = number of paediatricians, % given in brackets

LRA = Leukotriene receptor antagonists.

First choice Broncho dilators	
Salbutamol	10 (100)
Atrovent	0 (0)
Either	0 (0)
Choice of initial delivery devise	
Inhaler with spacer	9 (90)
Nebulisers	1 (10)
Either	0 (0)
% of children with viral wheeze started on oral steroids	
None	0 (0)
1-25	2 (29)
26-50	2 (29)
51-75	0 (0)
76-100	3 (42)
% of children with viral wheeze started on LRA	
None	6 (86)
1-25	1 (14)
26-50	0 (0)
51-75	0 (0)
76-100	0 (0)

Table 5: Acute management of wheeze by paediatricians who do not differentiate between PVW and wheeze with interval symptoms (Group2)

n = number of paediatricians, % given in brackets

LRA = Leukotriene receptor antagonists.

	PVW	Wheeze with interval symptoms
% of children started on inhaled steroids		
None	8 (21)	2 (6)
1-25	22 (58)	4 (12)
26-50	8 (21)	9 (27)
51-75	0 (0)	2 (6)
76-100	0 (0)	14 (49)
Do you advise parents to use short course high dose inhaled steroids during an acute wheezy attack?		
Always	1(2)	3 (7)
Some times	18 (41)	25 (57)
Never	25 (57)	16 (36)
% of children started on LRA		
None	36 (80)	13 (34)
1-25	9 (20)	22 (58)
26-50	0 (0)	3 (8)
51-75	0 (0)	0 (0)
76-100	0 (0)	0 (0)

Table 6: Out patient management of wheeze by paediatricians who differentiated between PVW and wheeze with interval symptoms (Group1)

n = number of paediatricians, % given in brackets

LRA = Leukotriene receptor antagonists.

% of children started on inhaled steroids	
None	0 (0)
1-25	4 (50)
26-50	3 (37)
51-75	1 (13)
76-100	0 (0)
Do you advise parents to use short course high dose inhaled steroids during an acute wheezy attack ?	
Always	1 (10)
Some times	6 (60)
Never	3 (30)
% of children started on LRA	
None	4 (50)
1-25	4 (50)
26-50	0 (0)
51-75	0 (0)
76-100	0 (0)

Table 7: Out patient management of wheeze by paediatricians who do not differentiate between PVW and wheeze with interval symptoms (Group2)

n = number of paediatricians, % given in brackets

LRA = Leukotriene receptor antagonists.

Signs	Points			
	0	**1**	**2**	**3**
Supra sternal retractions	Absent		Present	
Scalene muscle contraction	Absent		Present	
Air entry*	Normal	Decreased at bases	Widespread decrease	Absent/minimal
Wheezing*	Absent	Expiratory only	Inspiratory and expiratory	Audible without stethoscope/silent chest with minimal air entry
O2 saturation	≥ 95%	92%-94%	<92%	

Table 8: Pre School Respiratory Assessment Measure (PRAM)

PRAM is a validated assessment of the severity of Preschool wheeze in a hospital setting.

*If asymmetry between right & left more severe side is assessed

Chapter 3: Methods

3.1: Outline of study and Study Design

TWICS is a randomised, double blind placebo controlled trial of oral corticosteroids in children with PVW. The study was conducted in three hospitals in United Kingdom: Leicester Royal Infirmary, Queens Medical Centre and City Hospital Nottingham, and took place over 30 months from May 2005 to October 2007. Participants were recruited from children's admissions unit/ short stay unit/ paediatric accident & emergency unit and paediatric wards at the recruiting hospitals. All children recruited had an acute episode of wheeze associated with upper respiratory tract symptoms.

3.1.1: Inclusion criteria

The inclusion criteria were: all children aged 10 months to 60 months admitted to hospital with an acute episode of physician-diagnosed wheeze (Preschool viral wheeze). PVW was defined as wheeze associated with upper respiratory tract symptoms /signs of viral illness.

The diagnosis of PVW was made by the admitting paediatrician. The presence of an upper respiratory viral infection was determined clinically. Children were either referred to the hospital by the General practitioner (GP) or brought to the paediatric accident & emergency department by a parent or guardian. The lower age limit of 10 months was chosen to reduce the recruitment of infants with wheezing associated with bronchiolitis[111].

3.1.2: Exclusion criteria

Exclusion criteria were:

Children less than 10 months and more than 60 months

Children needing fluid resuscitation (more than or equal to 20 ml/Kg)

Bacterial sepsis (e.g.: bacterial pneumonia, meningitis)

Cystic fibrosis and bronchiectasis

Children with upper respiratory tract structural abnormality

Children on home oxygen

Children with heart disease

Children who were receiving immunosuppressive therapy or had an immune deficiency

Children who had active varicella infection or had recently been exposed to varicella

Children admitted for social reasons

Children with a history of chronic persistent wheeze with no evidence of a discrete deterioration in association with a clinical cold.

Although rare in the study population, children who received pre-treatment with oral steroids by the GP were not excluded from the study. Children with asthma were included in the study if they presented to hospital with an episode of wheeze, which was preceded with a viral illness.

3.1.3: Randomisation

A double blind, randomisation design that was stratified according to study centre. Study numbers were assigned sequentially and randomisation achieved by generating numerical codes in random permuted blocks of 20. Randomisation and packaging of placebo and prednisolone were done by Nova Laboratories Ltd, Leicester, UK. Placebo and prednisolone were packaged in identical capsules containing an identical volume of lactose in identical containers labelled with the patient's number only (For more information on trial medication see Section 3.5).

Recruiting doctors and nurses were masked to treatment allocation. Randomisation codes were locked in a hospital pharmacy department until the entry of all data was complete. Randomisation was applied to children who were found to be eligible and whose parents agreed to have them participate.

3.1.4: Subject recruitment

Children were recruited into the study by research fellow or doctors in paediatric accident & emergency department, short stay unit, admissions unit, or paediatric wards. Recruiting doctors were regularly trained & updated on recruitment and methodology of the study by the research fellow. Nursing and medical staff were updated on the progress of the trial once every 6 months.

Recruitment packs were kept in a TWICS trial folder in the short stay unit at Leicester Royal Infirmary and admissions unit at Queens Medical Centre & City Hospital Nottingham. They were serially numbered. Packs at Leicester Royal Infirmary were labelled LR1, 2, 3 and so on while packs at Queens Medical Centre & City Hospital were labelled as QMC 1, 2, 3 & City 1, 2, 3 respectively. All the trial packs were kept in one place in each centre to avoid the duplication and to minimise the error in recruitment. Each Recruitment pack contained invitation letter inviting parents to participate in the trial, parent information leaflet, consent form, GP letter, data entry sheets and symptom diary card (Appendices 3-8).

Trial medications were kept in a secure pharmacy cupboard in the short stay unit at Leicester Royal Infirmary and admissions unit at Queens Medical Centre & City Hospital, fulfilling all the Medicines and Healthcare Products Regulatory Agency (MHRA) requirements (For more information on trial medication see Section 3.5).

Children who presented to a hospital with wheezing on auscultation were screened for eligibility by a paediatrician after they had received 10 puffs of salbutamol, administered through a metered-dose inhaler and volumatic spacer (Allen and Hanburys) with a face mask, or nebulised salbutamol (2.5mg if the child was <3 years of age or 5.0 mg if the child was >3 years of age). Each centre kept a record of number of children who were screened.

If found fulfilling the inclusion criteria, parents were given an invitation letter inviting them to participate in the trial and information sheet. If parents agreed to participate, they were approached for written consent. The nature of the trial was explained to the parents and any concerns raised by the parents were clarified by the recruiting doctor.

Once consent was obtained, children received either oral corticosteroids or placebo for 5 days, along with inhaled bronchodilator therapy. The frequency and mode of delivery device was decided by the admitting clinician. During administration of the study drugs, a nurse broke open a white capsule containing either prednisolone or placebo and mixed the white powder with 10 ml of a strongly flavoured drink (usually black-currant flavoured).

The dose of prednisolone was 20mg for children aged 2-5 yr, and 10 mg for children under 2 yr [67]. In the study children from 10 months to 24 months received 10 mg trial medication while children from 25 months to 60 months received 20 mg trial medication. This dosing regime ensured that all children recruited to the study received at least 1mg/kg of prednisolone. Regime based on lower dosage was chosen to make sure younger children aged 10 months and 25 months in both age categories are not overdosed. Dosing regime based on mg/kg of weight was considered. However it is practically impossible to conduct such a large trial based on this regime as trial medications had to be prepared early. To ensure correct dose of medications, as per this regime, for children who may weigh from 6kg to 30 kg, trial medications with dosage ranging from 6mg to 30 mg or 12 mg to 60 mg will have to be made. This means randomisation of 24 to 48 different strengths of medication in a trial of 700 children.

Clinicians were allowed normal flexibility to direct all other aspects of acute hospital management in line with the BTS Guideline. Clinicians had the liberty to withdraw the child

from the study at any time and treat as they feel appropriate (i.e. replace the trial medication with systemic steroid).

Children were initially treated in the paediatric accident and emergency department, children's admissions unit or short stay unit. The hospitals' care pathway for preschool children with virus-induced wheezing is to discharge children home if they have no or minimal wheezing on auscultation after inhalation of salbutamol, if the oxygen saturation is more than 92% while breathing ambient air on pulse oximetry, and if the clinician judges that the child will remain clinically stable at home receiving inhaled salbutamol as required (up to a maximum of four to six puffs at 4-hour intervals through a metered-dose inhaler and volumatic spacer).

For children initially treated in the paediatric accident and emergency department and remaining symptomatic after the administration of salbutamol, clinicians either continued treatment in the emergency department or transferred the patient to a short-stay observation-and-assessment ward associated with the emergency department or to a paediatric ward. Similarly children who were initially seen in children's admissions unit or short stay unit (Children referred to the paediatric team by GP) were transferred to paediatric wards based on clinical assessment of severity of wheeze by the recruiting doctor. In some cases, selection of the treatment site was influenced by nonclinical factors, including the time of day and the availability of beds.

In this study, the treatment-and-observation policy was identical at all study centres, including the accident and emergency department, and monitoring was always done by nursing staff with paediatric training. The decision to discharge a patient from the hospital was based on the judgment of clinicians, taking into consideration the clinical variables described below (Section 3.2).

3.2: Data collection

At presentation, a standard proforma was completed recording age, gender, address, carers name and contact number (Appendix 7). Parents were given a history sheet to complete (Appendix 7). This contained information on the duration of current episode of wheeze, past history of wheeze including age of onset of wheeze, previous hospital admissions and GP visits and courses of oral steroids. Information of pre-existing co-morbidity, history of atopic disease (i.e., eczema, hay fever and food allergy), parental smoking, parental asthma and bronchiolitis as infant were obtained. Information on current treatment of wheeze (medication, mode of delivery and dose), new treatment or increasing dose of existing treatment and antibiotics in the week prior to recruitment was recorded. Dose and time of pre-treatment with oral steroids from the GP, if any were also recorded.

3.2.1: Baseline

Five minutes after patients who were enrolled in the study had received a dose of inhaled salbutamol, baseline variables were recorded. This included temperature, respiratory rate, heart rate, and the components of the preschool respiratory assessment measure (PRAM), a validated scale for preschool wheeze (Appendix 7). (See Section 3.3 for further details). In addition parents were provided with a diary card for reporting respiratory symptoms after discharge from the hospital. (See Section 3.4 for further details).

3.2.2: 4, 12 and 24 hours post admission

Attending doctor recorded temperature, respiratory rate, heart rate and PRAM components at 4 hrs in all children, and in those that remain hospitalised at 12 and 24hr. Children were reviewed every 4-6 hours to verify whether they were well enough to be discharged. The time at which clinician felt child was ready for discharge and the actual time of discharge were documented separately (Appendix 7). Complications recorded for the trial included admission

to intensive care, continuing hypoxia, withdrawal from the study (and reason for this whether clinician or parent preference), and protocol variation.

3.2.3: Discharge

The time of discharge was recorded by administrative personnel as part of normal hospital record keeping. This information was used to cross check the time of actual discharge recorded by the doctor in the data sheet. On discharge from the hospital, parents or guardians were provided with the remaining capsules to complete the course and were instructed in their use. They were also reminded to return the symptom diary card.

3.2.4: Post discharge

The clinical notes were reviewed to determine the frequency and dose of medication given during hospitalisation. Oxygen and intra venous fluid requirement were also recorded. Treatment during stay in hospital included all medications received from the time of randomisation till the time child was fit for discharge. Medications received after child was fit for discharge were included in the treatment during 7 days post discharge (Appendix 7).

A telephone follow up was carried out at 1 and 4 weeks post discharge. During the first phone call, parents were reminded to return the symptom diary card, and asked to identify the day when their child was “back to normal”. At 4 weeks, information was obtained on disruptions to parental work, readmission to hospital, re attendance to GP and if appropriate, the day when their child was considered to be “back to normal” (Appendix 7). The hospital Patient Administration System (PAS) was also used to check for re-admission to hospital in the month following discharge. The 7-day parental daily symptom diary was collected.

3.3: The Pre School Respiratory Assessment Measure (PRAM) Score

Assessment of response to treatment in children with wheeze should be ideally measured with objective markers like lung function measurements. This requires good coordination and technique is usually poor in pre school children. Further more this can be time consuming and is not feasible in large clinical trials. Hence researchers/clinicians rely on clinical signs and oxygen saturation. As the assessment and importance given to each clinical sign varies between clinicians this can be subjective. A validated clinical score can eliminate or minimise some of these issues. Even though this is not perfect, this is the best available measure to assess the response to treatment

The 12-point PRAM is a validated score for assessing asthma severity in pre school children [112]. This score has been validated against measure of lung function. The 5 PRAM variables include supra sternal retractions, scalene muscle contraction, air entry, wheezing and oxygen saturation. Score for each variable varies from 0 to 3, with a total score of 12 (Table 8).

Three of the five PRAM variables, i.e., supra sternal retractions, air entry and wheezing are clinical signs usually documented in routine clinical examination. When assessing air entry and wheeze if there is asymmetry between right and left lungs, the most severe side is rated. Fourth sign, contraction of scalene muscles is a sign of marked airway obstruction [112]. The scalene muscles are a group of three pairs of muscles (anterior, middle and posterior scalene) in the lateral neck extending from cervical vertebrae to first and second ribs. They originate from the lateral process of C3 to C7 vertebrae and inserts onto first and second ribs. The anterior and middle scalene elevates the first rib and rotates the neck to the opposite side where as posterior scalene elevates the second rib and tilt the neck to the same side [113]. Scalene muscles along with sternomastoid and trapezius are the accessory muscles of inspiration. When these muscles contract for tidal breathing - it is abnormal. Contraction of sternomastoid and trapezium, easy to recognize, is a late event where as contraction of scalene

muscles happens early. Scalene muscles are felt by standing behind the patient and placing the fingers over the scalenus behind the sternomastoid in the supraclavicular fossa. When the muscle contracts it can be recognized as narrow band of contracting muscle. Fifth variable of PRAM score, oxygen saturation, is measured using a pulse oximeter.

PRAM was assessed 5 minutes after the administration of a dose of inhaled salbutamol. Scores on the PRAM ranged from 0 to 12, with higher scores indicating a greater severity of respiratory distress. The severity of airway obstruction was interpreted as mild if score was less than 5, moderate if more than or equal to 5. In severe obstruction PRAM score was expected to be more than or equal to 9. Identifiable clinically meaningful improvement was represented by a change from baseline of more than or equal to 3 [112].

All recruiting clinicians received training in assessing the PRAM components. All training was done by the research fellow. After a teaching session on the PRAM components, each recruiting clinician was then asked to score an acutely wheezy preschool child under supervision. If necessary, further training was given. Internal consistency and inter-rater reliability was not formally assessed. Under similar acute clinical conditions the PRAM has good internal consistency (Cronbach a = 0.71) and inter-rater reliability (r=0.78)[114].

3.4: Symptom diary

Symptom diary questionnaires completed by the parents or their caregivers provide valuable data regarding the efficacy of asthma interventions in paediatric clinical trials. Recording symptoms in a diary is comparable with other more objective measures [115-117]. Data in adults from Malo et al.[118] suggested that diary recorded symptoms were as reliable as peak flow in detecting flare-ups in asthmatic patients. However validity of symptom diary card reporting was questioned by Falconer et al.[119]. Asking parents offers some measure of objectivity [120] although this may be inaccurate [121] or at odds with the child's report [122, 123]. There can also be

difference in parents and health professional's comprehension of the term wheeze [124-129]. Compliance with diaries is generally poor. Recall bias is a limitation of all symptom diary measurements as diaries can be retrospectively completed [130] and it is impossible to assess the accuracy of recordings. In spite of all the limitations, symptom diaries provide and are the only source for a more complete assessment of the effectiveness of asthma treatment in clinical trials.

To assess participant's respiratory status at home, parents were provided with a symptom diary card (Appendix 8). Each question and options were explained to the parents by the recruiting doctor and were asked to complete the diaries in the evenings at the same time every day to provide an accurate assessment of child's condition in the previous 24-hour period. On a scale of 0 to 3, the severity of night time and daytime symptoms and disruption of daytime activity were recorded once daily for 7 days [114]. Parents chose the score that best described symptom severity, and recorded frequency of use of inhaled medication. GP and hospital visit for 7 days post discharge were also recorded. Parental opinion on the usefulness of trial medication was also sought. At the end of 7 days symptom diary cards were returned in the free post envelope provided. Daily symptom score was the total of day, night and activity score. Symptom score was calculated as the mean for 7 days.

3.5: Trial Medications

Trial medications were in identical capsules containing white powder, labelled only with the subject number (Appendix 10). The capsules containing prednisolone were prepared by crushing prednisolone 25 mg tablets, mixing the crushed powder with lactulose and filling into size 0 opaque hard gelatine capsules. The capsules were tested for weight uniformity, prednisolone content and disintegration. Placebo capsules were prepared by filling lactulose into capsule shells identical to those used for prednisolone capsules. Placebo capsules were

also tested for weight uniformity, disintegration and absence of prednisolone. Trial medications had a shelf life of 12 months.

Randomisation and packaging of placebo and prednisolone was done by Nova Laboratories Ltd, Leicester, UK. Randomisation was done in a block of 20 patients for each strength investigated. Each block of 20 trial medications contained 10 placebo and 10 prednisolone bottles. Randomisation was performed based on a computer generated model. AJ, pharmacist at Nova Laboratories arranged the trial medications based on the computer generated model into block of 20. This was further cross checked by another pharmacist at Nova Laboratories before being delivered to the trial site.

Each trial medication bottle was numbered sequentially and contained 5 capsules. Bottle label contained information on the strength of the capsules and duration of treatment (once daily for 5 days) (Appendix 10). Before medication was given bottle and strength of the medication were crosschecked and signed by two persons involved in child's care. When the trial medication was given, participants name, date dispensed and trial site were written on the bottle and the medication bottle number was recorded on the data sheet. Following entry was made on the drug sheet: Trial medication (TWICS Trial) (Oral prednisolone or placebo) 20 or 10 mg once daily for 5 days.

Parents were advised that their child would be receiving either oral prednisolone medication or dummy medication. To deliver the medication, capsule was opened and the powder from the capsule was added to a small amount of fruit drink. When the first dose of medication was given parents were shown how to open the capsule. Occasionally children vomited the medication, but they were not given another dose.

All sets of trial medications were used with in the shelf life of 12 months. New set of trial medications were requested when 60% of the previous set was used up. These ensured medications were not made earlier than needed. During the conduct of the trial no formal stability assessment of the trial medications were made.

3.6: Randomisation of study subjects

Randomisation was performed when the trial medication was made as explained in section 3.5. Trial medication bottles were numbered from 1-700. Participating children were given trial medication based on their age group. In the first batch of medications, trial medications numbered 1-120 was 10 mg (for 10-24 month age group) and trial medications numbered 121-240 was 20 mg (for 25-60 months). The first child recruited in the trial was 22 months of age and received trial medication numbered 1. Next child in the age group 10 months to 24 months received trial medication numbered 2 and so on. Similarly first child in the age group 25 months to 60 months received trial medication numbered 121, second child in the same age category received trial medication numbered 122 and so on.

3.7: Adverse events

Children were monitored for adverse events during hospitalisation. Adverse events after discharge were monitored by telephone follow-up. An independent data and safety monitoring committee, whose members were not involved with the enrolment of patients, tracked any adverse events.

3.8: Patient not enrolled

Information on all children between 10 months and 60 months, admitted with PVW and not enrolled in the trial were recorded separately. Their age, gender, reason for not enrolling (i.e., fulfilled the exclusion criteria, not approached for consent, declined to take part etc.) and

triage observations (heart rate, temperature, respiratory rate and oxygen saturation) were recorded.

3.9: Ethics

Application for ethical approval for the study (COREC (Centre of Research Ethical Campaign) form A-C, letter of invitation, parent information leaflet, consent form, GP letter, study protocol and Curriculum Vitae (CV) of all investigators involved in the trial) was submitted to Multicentre Research Ethics Committee (MREC) on 18th of January 2005. Application was reviewed by the committee on 1st of February 2005. Over the phone clarifications were sought on the following issues 1. Treatment of children with severe wheeze not to be withheld due to their participation in trial 2. Children who are already in trial, if readmitted with another episode of wheeze should not be recruited again. After few minor amendments in the parent information leaflet final approval for the Leicester Royal Infirmary site was granted on 18th of February 2005. Local Research Ethics Committee (LREC) approval for recruiting patients at Queens Medical centre Nottingham and City Hospital Nottingham was obtained in November 2005.

3.10: Medicines and Healthcare Products Regulatory Agency (MHRA) approval

Following the MREC approval, MHRA approval for the study was sought. Clinical trial authorisation (CTA) application (Eudract Number: 2004-005124-40) was submitted along with the necessary documents on 1st of March 2005. Following few minor clarifications, MHRA approval was granted in April 2005.

3.11: Duration & conduct of the trial

Recruitment at Leicester Royal Infirmary site started in May 2005, while recruitment at Nottingham sites started in December 2005. Incidence of PVW clearly showed a seasonal trend with majority of children presenting in the months of September-February. Recruitment

to the trial lasted for 30 months with 700th patient recruited in October 2007. JP coordinated the day to day running of the trial across three centres, recruited 90% of patients at Leicester Royal Infirmary site and collected the data on children recruited at Leicester. A research nurse, Natasha Lafond, supervised the recruitment and was responsible for data collection at Nottingham sites.

I entered the trial data into the database. Each entry was done in a block of 50 children. Following the entry, I crosschecked all the variables entered once again. This was followed by random cross checks of 5 datasets by either NL or PK. Following the entry of 350 data sets, one further random cross check of 10 data sets was conducted.

3.12: Data & safety monitoring committee

A Data and safety monitoring committee was set up to monitor the safety of the trial and to assess the quality of data. Committee was chaired by Dr Jane Clark, Consultant Respiratory Paediatrician at Birmingham Children's Hospital and included Mr Jabu Sithole, Statistician from Nottingham University. Committee met once, half way through the recruitment, and expressed satisfaction with the quality of the data collected. No safety issues or adverse events were encountered in the trial.

3.13: Steering group

Steering group met once every 2 months during the entire duration of the trial and consisted of Prof Jonathan Grigg, Drs Monica Lakhanpaul, Alan Smyth, Jay Panickar, Paul Lambert and Natasha Lafond. The meetings were extremely helpful in dealing with the issues encountered in the day to day conduct of the trial.

3.14: Research governance

Research fellow and all doctors recruiting for the trial attended Good Clinical Practise (GCP) training course. An annual progress report on the conduct of the trial was submitted to LRI local research office and Asthma UK. Report detailed the progress of recruitment and safety issues encountered, if any.

3.15: Statistical analysis

The required power for the study was determined from a prospectively collected data on 208 preschool children presenting to the University Hospitals of Leicester National Health Service Trust with a physician-diagnosed attack of virus-induced wheezing. We calculated that 350 in each group would give a power in excess of 80% to detect a difference of 5 hours in the geometric mean of duration of hospital stay with a two-sided alpha level of 0.05. An interim analysis was not included in the statistical analysis plan. Differences in continuous outcomes between the two study groups were assessed by obtaining mean differences with 95% confidence intervals from a linear regression model incorporating the study centre as a variable. The mean duration of hospital stay was log transformed before analysis, since this variable was positively skewed. The treatment effect thus refers to the ratio of geometric means for the primary outcome. In addition, we calculated the difference in the median duration of hospital stay with 95% confidence intervals, which were obtained with the use of the bootstrap method[131]. The duration of hospital stay was also shown graphically with the use of Kaplan–Meier survival estimates (Figure 2). For other positively skewed variables, 95% confidence intervals for differences in means were obtained by the bootstrap method[131]. Differences between categorical variables were expressed as odds ratios with 95% confidence intervals, obtained from a logistic-regression model incorporating the study centre as a variable.

The only pre specified subgroup analysis involved children who were at increased risk for atopic asthma. This subgroup, which was based on the clinical index for an increased risk of asthma in preschool children reported by Castro-Rodriguez et al. [59] was defined as children with a history of four or more wheezing episodes who had a parent with asthma or who had physician-diagnosed eczema. There were two post hoc subgroup analyses, stratified according to PRAM score and age. For each subgroup analysis, heterogeneity was assessed by adding an interaction term with treatment to the model. PRAM scores at 12 and 24 hours were analyzed only for patients who were still in the hospital.

All analyses were performed with the use of Stata 10 statistical software, version 10.0. All P values are two-sided and have not been adjusted for multiple testing.

I outlined all the questions which needed to be answered. Along with Paul Lambert I decided on which statistical test is most appropriate for each question. Paul Lambert analysed the data.

Chapter 4: Results

4.1: Patients

1180 children were screened for study eligibility (Figure 1). Of these children, 162 did not meet the eligibility criteria. The majority of children who did not meet the inclusion criteria were judged by a clinician to be asymptomatic after a single dose of inhaled salbutamol, administered through a metered-dose inhaler and spacer (n=146, 90%). 14 children were noted to have other underlying respiratory pathology as chronic lung disease needing home oxygen, upper airway anomaly and were excluded. 2 children were diagnosed with sepsis after initial assessment (Table 9). Of the remaining 1018 children, 318 parents declined to participate.

A total of 700 children underwent randomisation. For three sequential children, the trial bottle number was not recorded and group assignment could not be determined, thus reducing the number of study participants to 697. Ten children who presented to the hospital on a second occasion were enrolled in error. These 10 children were assigned to receive a study drug, but data from the second admission were removed from the study database. All these children were brought to hospital by the parent who did not accompany the child in the first instance and hence were unaware of child's previous participation in the trial. The remaining 687 children were included in the intention-to-treat analysis; 343 children were assigned to receive prednisolone and 344 to receive placebo.

The primary outcome was not recorded for one child in the placebo group and for two children in the prednisolone group. Among the secondary outcome measures 4-hr PRAM was available in 316 children in the prednisolone group and 309 children in the placebo group. 280 children in the prednisolone group and 301 children in the placebo group returned the symptom diary card. 1 month readmission data was available in 283 and 303 children in prednisolone and placebo group respectively. Three attempts were made to contact the

families at the end of 4 weeks post discharge and remaining families were not contactable even after 3 attempts. 95% of families were contacted at the first attempt.

4.2: Baseline characteristics

Baseline characteristics of 687 children were analysed. The results do not include baseline data on the second admission of 10 children who had been recruited on a previous occasion and data for 3 children for whom study-group assignments could not be determined. However the baseline data for 3 children who were randomly assigned to receive a study drug but for whom primary-outcome data were not recorded were included. Data are missing for patients for whom a parent or guardian was unsure of certain baseline variables.

4.2.1: Demography

63% (216/344) of children in the placebo group and 66% (227/343) of children in the prednisolone group were boys. The mean age of patients in the trial was 26 months (placebo vs. prednisolone - 26.2 ± 14.7 vs. 25.8 ± 13.3), with age at first onset of wheezing being 15.8 and 16.6 months in placebo and prednisolone group respectively. Two third of children in both groups (placebo vs. prednisolone - 68% vs. 63.6%) had at least one previous episode of wheeze (Table 10).

4.2.2: Personal & family history

59 out of 333 (17.7%) children in the placebo group reported interval symptoms while 47 out of 330 (14.2%) in the prednisolone group had cough and wheeze not associated with cold. 16.3% of children in the placebo group and 18.9% of children in the prednisolone group had a diagnosis of asthma at the time of recruitment. 40% and 8% of children in both arms had past history of eczema and hay fever respectively. 22 children (6.6%) in the placebo group and 33 (10.1%) children in the prednisolone group had an allergic reaction to food in the past. One out of 4 children in both arms (placebo vs. prednisolone - 25.9% vs. 22%) had past history of

bronchiolitis. 25% of children in both arms had family history of maternal and paternal asthma. One out of 3 children in both arms had smokers in household (Table 11).

4.2.3: Frequency & severity of wheeze

Parents were asked about the number of episodes of wheeze in the 12 months prior to recruitment and past number of hospital admissions for wheeze. One in three children (placebo vs. prednisolone - 36.7% vs. 38.6%) did not report any episode of wheeze, where as a similar number reported between 1 and 3 episodes (placebo vs. prednisolone – 36.1% vs. 31.6%). 20 % of children in both arms had 4-6 episodes of wheeze and a minority (7.1% and 11% in placebo and prednisone group respectively) reported more than 6 attacks.

Majority (80%) of children in both arms did not have any previous hospital visit for wheeze, while 15% of children had either one or two hospital visits. 12 children (3.6%) in the placebo group and 21 children (6.3%) in the prednisolone group had 3 or more previous presentations to hospital with acute wheezing (Table 12).

4.2.4: Medications

Half of the children in both arms were using salbutamol inhalers as required, where as one in five children were prescribed prophylactic inhaled corticosteroids either by GP or hospital doctor. One child in the placebo group and 2 children in the prednisolone group were on regular montelukast. 73% of children in both arms haven’t had any short course of oral steroids for wheeze in the previous 12 months, while 20% received one or two courses. 19 (5.8%) children in the placebo group and 25 (7.5%) children in the prednisolone group had 3 or more courses of oral steroids (Table 13).

4.2.5: PRAM score

Baseline PRAM score was assessed on 679 children. Mean scores were 4.27 (340 children) and 4.32 (339 children) in the placebo and prednisolone group respectively (Table 13). There were no significant differences between the two study groups in baseline demographic characteristics and PRAM scores.

4.3: Primary outcome

Primary outcome measure was recorded in 343 children in the placebo group and 341 children in the prednisolone group. The time to signoff for discharge and actual discharge from the hospital was relatively short in both the placebo group and the prednisolone group. The median duration of time to signoff for discharge and actual discharge from the hospital was 12.0 hours and 13.9 hours respectively in the placebo group and 10.1 hours and 11.0 hours respectively in the prednisolone group. There was no significant difference between the study groups in the time to actual discharge from the hospital (ratio of geometric means, 0.90; 95% confidence interval [CI], 0.77 to 1.05; P = 0.18) or in the time to signoff for discharge (ratio of geometric means, 0.89; 95% CI, 0.76 to 1.05; P = 0.16) (Table 14). The duration of hospital stay is also shown graphically with the help of Kaplan-Meier survival estimate (Figure 2).

4.4: Secondary outcomes

4.4.1: Outcomes during Hospitalisation

There was no difference in the treatment site between the groups with 45% of children being managed in the observation ward (placebo vs. prednisolone 151 (43.9%) vs. 157 (45.8%)) and 55% managed in the paediatric ward (placebo vs. prednisolone 190 (55.2%) vs. 185 (53.9%)). 3 children in the placebo group and 1 child in the prednisolone group was exclusively managed in the emergency department (Table 15). There was no significant difference

between the groups in the number of salbutmol actuations administered in the hospital or in PRAM scores at 4 to 24 hours (Table 15).

341 children in the placebo arm had a mean number of 66.70 salbutamol actuations compared to 52.8 actuations in the prednisolone group (342 children). Mean PRAM score in placebo and prednisolone group at 4 hours post randomisation were 2.74 (assessed in 309 children) and 2.48 (assessed in 316 children) respectively. Similarly there was no difference between two groups in PRAM scores at 12 and 24 hours. (placebo vs. prednisolone - 12 hours - 2.28 ± 2.03 vs. 2.49 ± 1.98: 24 hours - 1.58 ± 1.64 vs. 1.52 ± 1.75). Similar number of patients in both arms received antibiotics during their stay in hospital (placebo vs. prednisolone -13% vs. 11.9%) and substitution of a study drug and introduction of definitive systemic corticosteroid (placebo vs. prednisolone - 6.2% vs. 4.5%) (Table 15).

4.4.2: Outcomes after discharge from the Hospital

Data on outcome after discharge from hospital were obtained from symptom diary card and telephonic contact with the families. 301 parents (88%) in the placebo group and 280 parents (82%) in the prednisolone group returned the symptom diary card. Majority (90%) of them returned the diary within 3 weeks of discharge and all of them returned the diary within 4 weeks post discharge. Some of the diary cards went missing in the post.

Day time symptom score was analysed in 228 children in the placebo group and 204 children in the prednisolone group. Night time score was completed by 234 and 204 parents in the placebo and prednisolone group respectively. Quality of data was poor in the remaining diary cards. Some diary cards were returned without filling any of the variables. There were no significant differences between the two study groups in parent-assessed 7-day mean symptom scores, the time to return to normal activities, and the number of salbutamol actuations given at home during a 7-day period.

Patients in the placebo group had a mean ± SD day time score of 1.10 ± 0.65 which wasn't significantly different to the children in the prednisolone group 1.00 ± 0.69. Similarly night time scores were 0.99 ± 0.81 and 0.84 ± 0.77 respectively in placebo and prednisolone group. In the 7 days following discharge from hospital, 222 children in the placebo arm had a mean ± SD number of 10.8 ± 9.5 actuations of salbutamol, while 198 children in the prednisolone arm had a mean of 10.60 ± 8.3 actuations. Patients in both arms took 5 days to return to normal self (placebo vs. prednisolone - 5.10 ± 3.84 vs. 5.13 ± 3.90) . The two study groups also did not differ significantly in the number of readmissions to the hospital for wheezing within a month (6.3% in the placebo group and 7.4% in the prednisolone group) (Table 16).

4.5: Subgroup analysis

A total of 124 children (58 in the placebo group and 66 in the prednisolone group) were classified as being at high risk for asthma at school age. In this subgroup, there was no significant difference between the placebo group and the prednisolone group in the duration of hospitalisation and no evidence of a differential treatment effect, as compared with children who were not in the high-risk group (test for interaction, P = 0.31). In a post hoc analysis, there was no evidence of a significant differential treatment effect for the time to actual discharge stratified according to the PRAM score or age (Table 17).

4.6: Adverse events

No clinically significant adverse events were reported to the patient safety committee. In one child in the prednisolone group, parents attributed excess vomiting to the study drug and discontinued the medication after discharge from the hospital.

In summary there was no significant difference between two study groups for any of the outcome measures or adverse events.

Total no: of children excluded	162
Children judged to be asymptomatic after single dose of inhaled salbutamol	146 (90%)
Children with chronic lung disease needing home oxygen	6
Children with upper airway disease	4
Children with other chronic respiratory problems	4
Children diagnosed with sepsis after screening for study eligibility	2

Table 9: Children not meeting the eligibility criteria for TWICS trial

Characteristic	Placebo (N=344)	Prednisolone (N=343)
Male sex-no. (%)	216 (62.8)	227 (66.2)
Age-months	26.2 ± 14.7	25.8 ± 13.3
Previous wheezing-no. /total no. (%)	229/337 (68.0)	211/332 (63.6)
Age at first onset of wheezing		
No. of patients	326	327
Mean -months	15.8 ± 12.3	16.6 ± 12.0

Table 10: Baseline characteristics of the patients – Demography

Plus-minus values are means ± SD.

Characteristic	Placebo (N=344)	Prednisolone (N=343)
Coughing or wheezing without a cold during previous year-no. /total no. (%)	59/333 (17.7)	47/330 (14.2)
Conditions previously diagnosed by physician-no. /total no. (%)		
Asthma	55/337 (16.3)	63/333 (18.9)
Eczema	132/335 (39.4)	136/330 (41.2)
Hay fever	24/324 (7.4)	26/324 (8.0)
Food allergy	22/331 (6.6)	33/327 (10.1)
Bronchiolitis	85/328 (25.9)	71/323 (22.0)
Family history of asthma-no. /total no. (%)		
Mother	82/337 (24.3)	87/327 (26.6)
Father	80/333 (24.0)	83/326 (25.5)
Smokers in household-no. /total no. (%)	121/337 (35.9)	117/331 (35.3)

Table 11: Baseline characteristics of the patients –Personal & family history

Characteristic	Placebo (N=344)	Prednisolone (N=343)
No .of wheezing attacks in the previous year-no. /total no. (%)		
0	119/324 (36.7)	127/329 (38.6)
1-3	117/324 (36.1)	104/329 (31.6)
4-6	65/324 (20.1)	62/329 (18.8)
6-10	18/324 (5.6)	23/329 (7.0)
>10	5/324 (1.5)	13/329 (4.0)
No. of previous presentations to hospital with acute wheezing –no. /total no. (%)		
0	271/333 (81.4)	260/330 (78.8)
1-2	50/333 (15.0)	49/330 (14.8)
3-4	9/333 (2.7)	13/330 (3.9)
≥5	3/333 (0.9)	8/330 (2.4)
Parent reported fever associated with admission symptoms on admission – no. /total no. (%)	99/333 (29.7)	101/329 (30.7)

Table 12: Baseline characteristics of the patients – Frequency & severity of wheeze

Characteristic	Placebo (N=344)	Prednisolone (N=343)
Previously prescribed medication-no. /total no. (%)		
Inhaled salbutamol as required	191/340 (56.2)	172/340 (50.6)
Daily inhaled corticosteroids	65/340 (19.1)	61/340 (17.9)
Oral montelukast	1/340 (0.3)	2/340 (0.6)
No of courses of oral corticosteroids for wheezing in the previous year-no. /total no. (%)		
0	240/328 (73.2)	242/330 (73.3)
1-2	69/328 (21.0)	63/330 (19.1)
3-4	17/328 (5.2)	14/330 (4.2)
≥5	2/328 (0.6)	11/330 (3.3)
Baseline PRAM score		
No. of patients	340	339
Mean-units	4.27 ± 2.18	4.32 ± 2.31

Table 13: Baseline characteristics of the patients – Medications & PRAM score

Plus-minus values are means ± SD.

Duration	Placebo	Prednisolone	Difference (95% CI)	P Value
Interval between presentation and signoff for discharge				
No. of patients	342	340		
Median (hr)	12.0	10.1	-1.9 (-6.5 to 4.1)	0.16
Log_e mean	2.40 ± 1.11	2.28 ± 1.02		
Ratio of geometric means (95% CI)	NA	0.89 (0.76-1.05)		
Interval between presentation and actual discharge				
No. of patients	343	341		
Median (hr)	13.9	11.0	-2.9 (-8.7 to 2.4)	0.18
Log_e mean	2.46 ± 1.09	2.36 ± 1.02		
Ratio of geometric means (95%CI)	NA	0.90 (0.77-1.05)		

Table 14: Primary outcome - Duration of Hospitalisation

Plus-minus values are means ± SD. NA denotes not applicable.

Variable	Placebo	Prednisolone	Difference (95% CI)
Treatment site-no. (%)			
Exclusively in emergency department	3 (0.9)	1 (0.3)	
On observation ward	151 (43.9)	157 (45.8)	
On paediatric ward	190 (55.2)	185 (53.9)	
Use of salbutamol			
No. of patients	341	342	
Total metered-dose inhaler actuations-no.	66.70 ± 88.10	52.80 ± 74.50	-14.08 (-26.62 to 1.54)
PRAM Score			
At 4 hr			
No. of patients	309	316	
Score-units	2.74 ± 2.30	2.48 ± 2.20	-0.29 (-0.65 to 0.06)
At 12 hr			
No. of patients	163	149	
Score-units	2.28 ± 2.03	2.49 ± 1.98	0.20 (-0.24 to 0.64)
At 24 hr			
No. of patients	97	65	
Score-units	1.58 ± 1.64	1.52 ± 1.75	-0.06 (-0.57 to 0.51)
Antibiotics administered in hospital- no./total no.(%)	43/331 (13.0)	40/337 (11.9)	
Substitution of study drug with corticosteroid-no./total no.(%)	19/305 (6.2)	13/288 (4.5)	

Table 15: Secondary outcomes during Hospitalisation

Plus-minus values are means ± SD.

Variable	Placebo	Prednisolone	Difference (95% CI)
Respiratory-symptom score at 7 days			
Day time			
No. of patients	228	204	
Mean score-units	1.10 ± 0.65	1.00 ± 0.69	-0.06 (-0.18 to 0.07)
Night time			
No. of patients	234	204	
Mean score-units	0.99 ± 0.81	0.84 ± 0.77	-0.14 (-0.29 to 0.01)
Actuations of salbutamol at 7 days			
No. of patients	222	198	
Mean no.	10.80 ± 9.50	10.60 ± 8.30	-0.24 (-1.95 to 1.45)
Time to return to normal activities			
No. of patients	301	280	
No. of days	5.10 ± 3.84	5.13 ± 3.90	0.06 (-0.59 to 0.67)
Hospital readmission for wheezing within 1 moth after discharge-no. /total no. (%)	19/303 (6.3)	21/283 (7.4)	

Table 16: Secondary outcomes after Discharge from the Hospital

Plus-minus values are means ± SD.

	Placebo	Prednisolone	Ratio of geometric means (95%CI)	Test for interaction
Higher or lower risk of developing school-age asthma*				
Lower risk	N=272	N=261	0.92 (0.77 to 1.11)	P=0.31
Higher risk†	N=58	N=66	0.76 (0.52 to 1.10)	
Age group				
10 -24 months	N=191	N=193	0.83 (0.67 to 1.03)	P=0.12
25-36 months	N=63	N=68	0.76 (0.54 to 1.07)	
37- 60 months	N=89	N=90	1.21 (0.89 to 1.65)	
PRAM Score				
0 to 4	N=198	N=198	0.83 (0.69 to 1.00)	P=0.81
5 to 8	N=130	N=119	1.04 (0.83 to 1.30)	
9 to 11	N=11	N=20	0.89 (0.52 to 1.52)	

Table 17: Sub-group analysis for time to actual discharge

*Pre-specified subgroup analysis.

†Children at higher risk of developing school-age asthma have 4 or more wheezing episodes and either a parental history of asthma or physician-diagnosed asthma, based on the score by Castro-Rodríguez et al.[59]

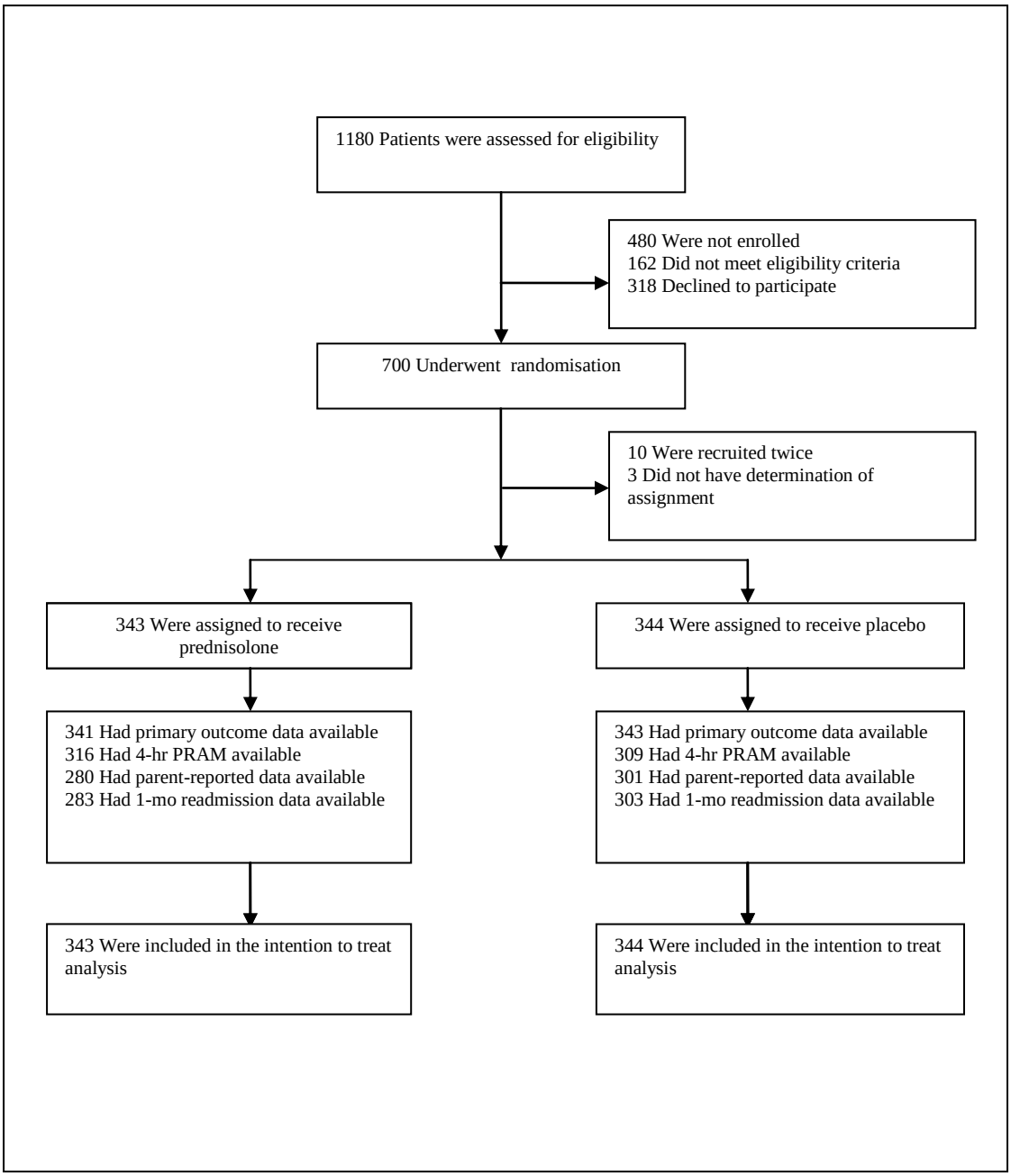

Figure 1: Enrolment and Outcomes

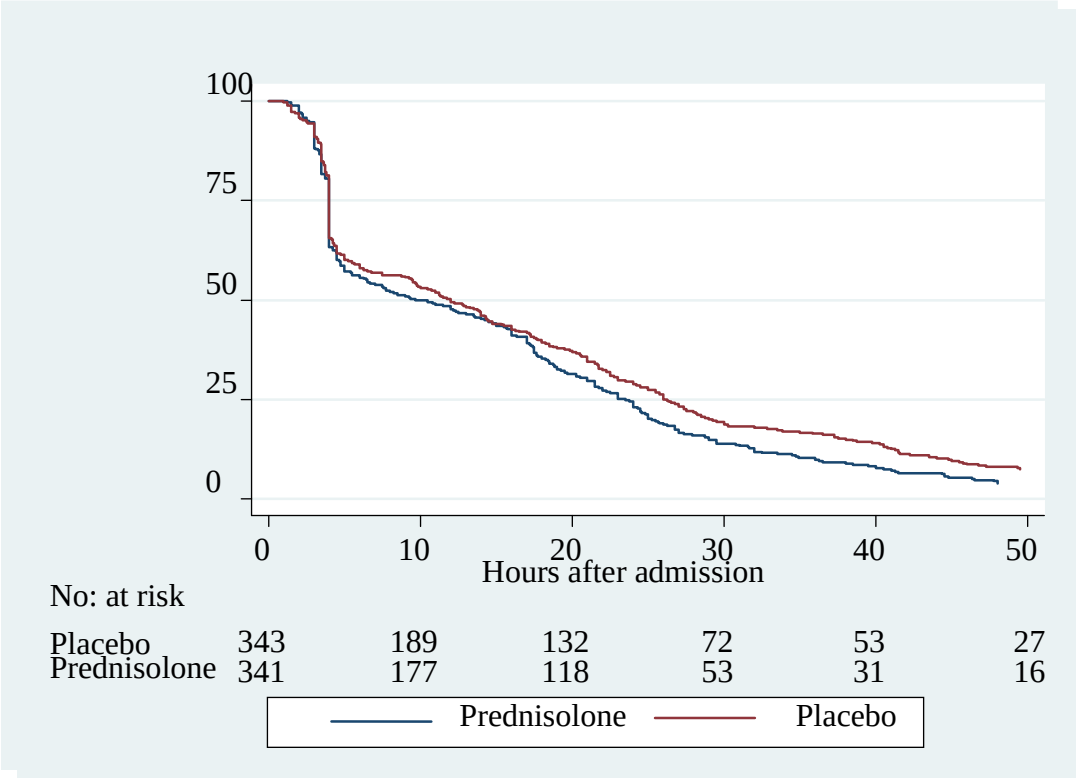

Figure 2: Kaplan-Meier estimates of the proportion of children remaining in the hospital.

Chapter 5: Discussion

In this three-centre trial of a 5-day course of oral prednisolone for preschool children with an attack of virus-induced wheezing, we found no significant reduction in the duration of the actual hospital stay, the interval between hospital admission and signoff for discharge, PRAM scores at any interval, 7-day parent-reported scores of symptom severity, and readmission to the hospital within 1 month after discharge.

5.1: Comparison with other studies

Our study results are consistent with the findings of no significant effect of a 5-day course of oral prednisolone in a previous community-based study of parent-initiated oral prednisolone for virus- induced wheezing among preschool children[78] . However, two studies have reported a beneficial effect of systemic corticosteroids in preschool children who presented to the hospital with acute wheezing. First, Csonka et al.[77] assessed a 3-day course of oral prednisolone (at a dose of 2 mg per kilogram of body weight per day) in 230 children under 3 years of age who presented to the hospital with virus-induced wheezing. Although corticosteroid treatment did not significantly reduce the proportion of children who were still hospitalised after 4 hours, significantly fewer children receiving corticosteroids required additional treatment in the hospital than in the placebo group. Second, Tal et al.[108] assessed the efficacy of a course of intramuscular methyl prednisolone (at a dose of 4 mg per kilogram) in 70 children who were 7 months to 54 months of age and who presented to the hospital with acute wheezing. The investigators reported that more children who received corticosteroids were discharged at 3 hours than those in the placebo group.

A major difference between these two studies and our study is that we included the PRAM score, a measure that has been validated against preschool lung function [112] and that has a good internal consistency and reliability among raters[114]. For short-term outcomes, there was

no significant difference between the two study groups in the 4-hour PRAM score and in the proportion of children who had been discharged home by 6 hours. The initial PRAM results suggest that the majority of children had mild-to-moderate wheezing, rather than severe wheezing[114]. However, PRAM scores were assessed after the administration of high-dose inhaled salbutamol and therefore did not reflect the maximum severity of wheezing. No significant effect of prednisolone was found in the longer-term outcomes, as assessed by parents after discharge, although these results were limited by the lack of validation of parent-assessed symptom scores against lung function.

The most likely explanation for the difference between our negative result and the positive results reported in other studies is that the majority of children who were recruited into our trial did not have the classic atopic asthma phenotype that is responsive to a short course of oral corticosteroids[104]. This explanation is supported by robust epidemiologic data showing that acute wheezing is not associated with atopy in a majority of affected children[22], and that it has a high likelihood of complete resolution by school age[132]. Many clinicians justify the routine treatment of all preschool children who present with virus-induced wheezing in order to preclude overlooking potentially responsive subgroups[133]. One putative corticosteroid-responsive subgroup is the small minority of preschool children in whom atopic asthma will develop at school age[22, 132]. To date, no predictive index for the development of asthma at school age has proved to be sufficiently accurate to be clinically useful in preschool children. However, in a subgroup analysis using the combination of variables reported by Castro-Rodriguez et al.[59] we found no evidence of responsiveness to corticosteroids in children who were at statistically high risk for asthma at school age.

Negative result of our trial on oral steroids, however cannot be extrapolated to very high doses of inhaled steroids. As described in section 2.1.3 studies using episodic high dose inhaled corticosteroids[71-74] have reduced the use of rescue oral corticosteroids, hospital visits

and duration of symptoms in children with PVW. It is unclear why these studies have shown a positive benefit for treatment with short course of high dose inhaled steroids in a population not at high risk of developing atopic asthma.

5.2: Limitations of the study

5.2.1: Subjects

We did not collect clinical data from the substantial proportion of children whose parents declined to have them participate in the study. Hence it remains possible that we selected children whose risk for atopic asthma was lower because of either increased symptom severity or parental perception of an increased risk of atopic asthma.

Identification of subgroup of children with increased risk for atopic asthma was based clinical history (children with a history of four or more wheezing episodes who had a parent with asthma or who had physician–diagnosed eczema) .We did not assess blood immunoglobulin E levels. However, recent data from the longitudinal German Multicenter Allergy Study suggest that blood markers of atopy have poor sensitivity and poor positive predictive value for school-age asthma[132].

It is also important to note that we have not ruled out a small difference between the two study groups, since the lower bound of the 95% confidence interval for the time to signoff for discharge was −6.5 hours. From our data, we calculated that the demonstration of a lack of effect of prednisolone would require a trial enrolling 4400 children to show that those given prednisolone had duration of hospital stay that was within approximately 2 hours of those in the placebo group.

5.2.2: Identification of viruses

We did not perform polymerase-chain-reaction analysis, immunofluorescence, or viral cultures to identify viruses associated with upper respiratory infections. An infecting virus is detected in up to 95% of preschool children with clinical virus induced wheezing[18], and clinical assessment alone is therefore a valid method of diagnosis. However, a recent study has raised the possibility of a differential response to corticosteroids as a function of the infecting virus[133]. Jartti et al.[106] performed a randomised, placebo-controlled trial of oral prednisone (at a dose of 2 mg per kilogram per day for 3 days) in children 3 months to 16 years of age presenting to the hospital with acute wheezing. In the subgroup of preschool children, oral prednisolone did not significantly reduce the primary outcome of the time to signoff for discharge[106]. However, in a secondary analysis, prednisolone treatment was associated with significantly fewer relapses for wheezing after discharge in the subgroup infected with rhinovirus[106]. Subsequently, post hoc analyses reported that prednisolone reduced the duration of symptoms and subsequent recurrent wheezing in rhinovirus-infected children[107, 134]. No trial has used virus-associated specificity to oral prednisolone as a primary outcome, and evidence for this phenomenon remains weak, since it is derived from post hoc, secondary analyses of subgroups of children in a small trial.

5.2.3: Trial medications

Despite the best efforts, some of the children may not have taken the trial medications at home. While in hospital, medications were administered by a nurse. At the time of discharge, parents were given clear instructions on the dose and duration of treatment. However it is possible that some children may not have received full duration of treatment. This can be due to either parents forgetting to give child the medications or child getting symptomatically better with complete disappearance of wheeze. Occasionally children vomited the trial medication and they were not given another dose as each trial bottle contained only 5 days of

medications. Hence some of our study population may not have received full duration of treatment.

TWICS study used a dosing regimen based on age group (10mg of trial medication for children aged 10months - 24 months and 20 mg for children aged 25 months-60 months). The drawback of this regime is that older children in both age groups may have received trial medication less than 1mg/kg hence reducing the efficacy of the treatment. No formal assessment of the stability of trial medication was done before administration of medication. Hence it may also be possible that trial medications at the time of administration may not have been as effective as it was at the time of manufacturing. However all the trial medications were used before the shelf life of 12 months. Primary outcome measure of our study, i.e, duration of stay in hospital was 12 hours. This is less than the time taken by corticosteroids to have an effect. Hence it is possible that in our study may not have been long enough to detect a noticeable difference in the outcome.

5.3: Future trials

Our study did not show any benefit in the use of oral prednisolone in the acute management of PVW even in the high risk group of children identified based on criteria by Castro-Rodriguez et al. However there may have been children in our study population who will benefit from oral corticosteroid therapy. Future studies should target these children. Challenge will be to identify them. Our suggestion is to use the criteria used in the Dutch birth cohort study[24] where they identified 1.5% symptomatic wheezy children (37/2171) with a score of more than 35, a cut-off that was highly specific for subsequent school age asthma. If we were to recruit 700 children at risk of developing school age asthma based on these highly specific criteria, the trial will have to screen 25,000 symptomatic children. A trial of this size will need cooperation of many centres in different countries.

5.4: Recommendations

Based on our study results, our recommendation is, acute mild to moderate episode of pre school viral wheeze should not be treated with short course oral prednisolone. If oral prednisolone is to be given, it should be reserved for small group of Pre School children admitted to hospital with severe episode of wheeze or with clinical features suggestive of atopic asthma. Our study has been taken as reference point by GINA (Global Initiative For Asthma) in arriving at the current recommendation for the use of oral corticosteroids in acute management of viral induced wheeze in children less than 5 years (Figure 3).

5.5: Conclusion

In conclusion, in a large, randomised, double blind trial of a 5-day course of oral prednisolone for preschool children with virus-induced wheezing who presented to the hospital, we found no evidence that a short course of an oral corticosteroid significantly shortened the duration of hospitalisation or significantly reduced markers of the severity of symptoms, as assessed by either physicians or parents. Our results suggest that oral prednisolone should not be routinely given to preschool children presenting to the hospital with acute, mild-to-moderate virus-induced wheezing.

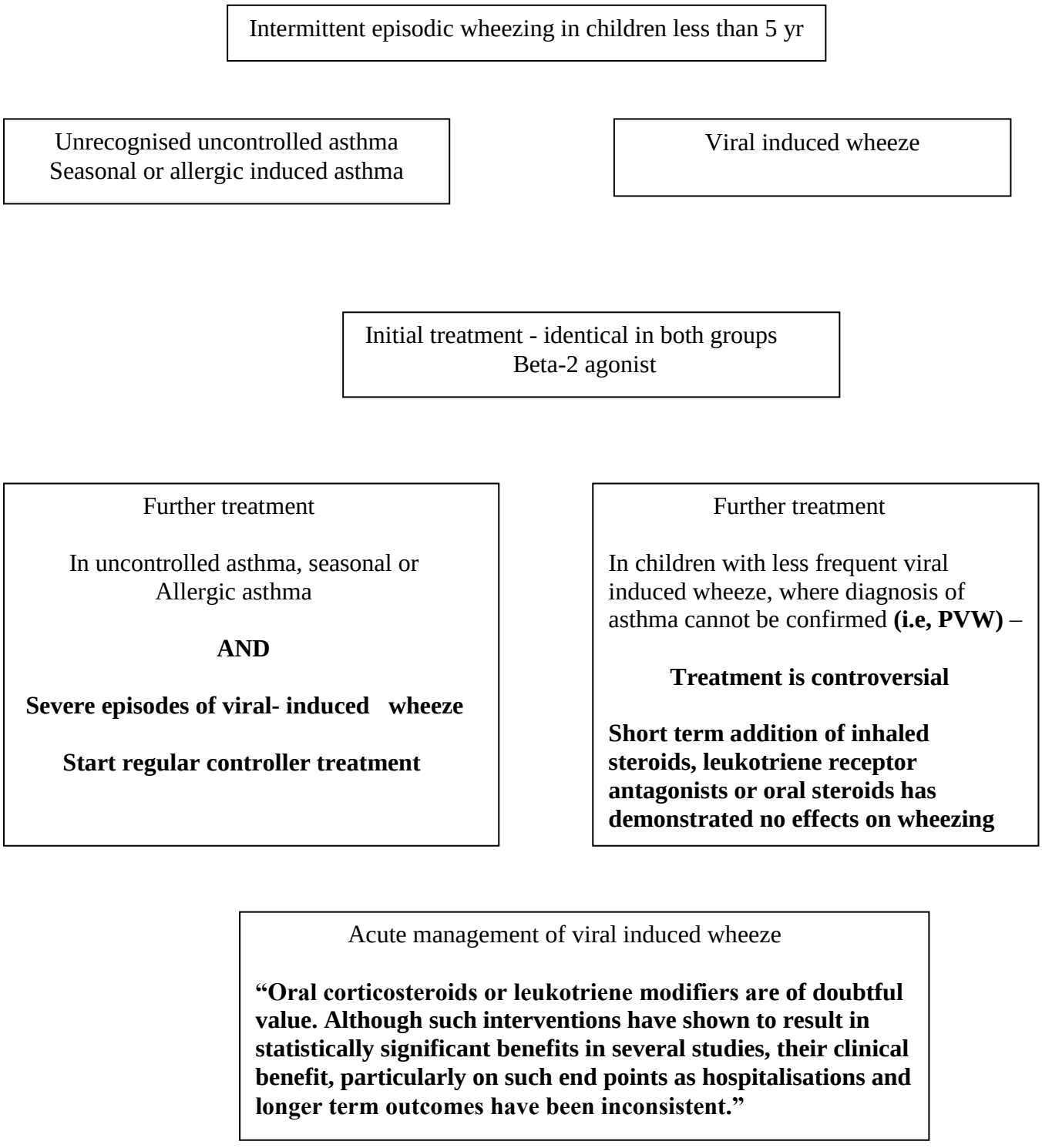

Figure 3: Summary of GINA recommendations for management of intermittent episodic wheezing in children less than 5 years (Specifically Viral induced wheeze).

PART 2

Acknowledgements

I would like to sincerely thank following people, without whom this thesis would not have been possible.

Prof Jonathan Grigg – for his support, encouragement and guidance through out the project. Prof Grigg designed the study and I would like to sincerely thank him for all the help and faith he had in me in conducting this trial.

Dr Monica Lakhanpaul – for her kind support and advice throughout the project.

Dr Paul C Lambert – for his assistance with statistical analysis.

Dr Priti Kenia – for helping me in completing the recruitment and data collection.

Dr Alan Smyth - for his support throughout the project.

Natasha Lafond – for coordinating recruitment and data collection at Nottingham sites.

Dr Jane Clarke – for chairing data and safety monitoring committee.

David Turner of NOVA laboratories – for timely delivery of trial medications.

Sarah Pegg & Sarah Peck, clinical trials pharmacists at Leicester Royal Infirmary – for the guidance in storage and delivery of trial medications.

All paediatric consultants at Leicester Royal Infirmary, Queens Medical Centre and City Hospital Nottingham – for letting me recruit children admitted under their care for the trial.

My sincere gratitude to all parents and children who participated in the trial, without whom this study would not have been possible.

Special thanks to all doctors who helped me in recruiting and data collection.

A special thanks to all nursing staff in accident and emergency unit, short stay unit, paediatric admissions unit and paediatric wards at Leicester Royal Infirmary, Queens Medical Centre and City Hospital Nottingham for their constant help in the conduct of the trial.

Special thanks to all ward clerks who helped me in tracing case notes.

Asthma UK - for their financial support.

Appendices

Appendix 1: Publications and presentations resulting from this thesis

Publications:

Panickar J, Lakhanpaul M, Lambert PC, Kenia P, Stephenson T, Smyth A, Grigg J. Oral prednisolone for preschool children with acute virus-induced wheezing.
N Engl J Med. 2009; 360(4):329-38.

Panickar JR, Grigg J. Controversies in the management of Pre School viral wheeze
Paediatr Respir Rev. 2006; 7(4):293-8.

Presentations:

Panickar J, Lakhanpaul M, Lambert PC, Kenia P, Stephenson T, Smyth A, Grigg J. Oral steroids in children hospitalised for Viral wheeze: A Randomised double-blind placebo-controlled trial (Treatment Of Wheeze In Children With Steroids, TWICS Study) British Paediatric Association, University of York, April 14-17, 2008. Arch Dis Child 2008; 93:A41-A42.

The study findings have been presented at various other regional, national and international meetings.

Appendix 2: Clinician Questionnaire

10-10-2005.

Dr Jay Panickar,
Room 514A,
Robert Kilpatrick Clinical sciences Building,
Leicester Royal Infirmary,
Leicester.

Dear Dr,

RE: Questionnaire survey on the management of Preschool viral wheeze.

We are currently conducting a therapeutic trial for preschool children (1-5 years) admitted to hospital with an attack of wheeze triggered by viral infections (pre-school viral-wheeze). Would it be possible to answer some questions about your current approach to this condition and return it in the enclosed self-addressed envelope? The questionnaire should only take couple of minutes to fill in.

Yours faithfully,

Jay Panickar MRCPCH,
Clinical Research Fellow in Respiratory Paediatrics,
Leicester Children's Asthma Centre, University of Leicester.

Definition of preschool viral wheeze (PVW): An episode of wheeze in a child aged 1 to 5 years of age that is triggered by a viral cold (defined by signs and symptoms).

Do you see children with attacks of preschool viral wheeze? YES ☐ No ☐

If YES - please answer the questions below.

Do you distinguish between Preschool children who wheeze exclusively with viral infection with no interval symptoms from Preschool children who wheeze with viral illness and with other triggers e.g.: exercise, allergens etc? YES ☐ No ☐

If NO Answer BOX 1 **IF YES Answer BOX 2**

BOX 1

1. In the management of Preschool children who wheeze with viral infection and with other triggers (e.g.: exercise, allergens etc):

	Management of acute wheezy episode			
1a	What percentage of children with PVW do you start oral steroids?			
1b	Usual dose of oral steroids	1 mg/kg ☐	2mg/kg ☐	Other ☐
1c	Usual duration of oral steroids	1day ☐	3days ☐	5days ☐
1d	What percentage of children with PVW do you start oral montelukast?			
1e	First choice bronchodilators	Salbutamol ☐	Atrovent ☐	
1f	Choice of initial delivery device	Nebuliser ☐	Inhaler with spacer ☐	
	Clinic (Out patient) long-term management			
1g	What percentage of children with PVW do you start inhaled steroids?			
1h	Do you advise parents to use short course high dose inhaled steroids during an acute attack of PVW?	Always	Some imes	Never
1i	What percentage of PVW children do you start oral montelukast?			

BOX 2

1.In the management of Preschool children who wheeze exclusively with viral infection with no interval symptoms:

	Management of acute wheezy episode			
1a	What percentage of children with PVW do you start oral steroids?			
1b	Usual dose of oral steroids	1mg/kg ☐	2mg/kg ☐	Other ☐
1c	Usual duration of oral steroids	1day ☐	3days ☐	5days ☐
1d	What percentage of children with PVW do you start oral montelukast?			
1e	First choice bronchodilators	Salbutamol ☐	Atrovent ☐	
1f	Choice of initial delivery device	Nebuliser ☐	Inhaler with spacer ☐	
	Clinic (Out patient) long-term management			
1g	What percentage of PVW children do you start inhaled steroids?			
1h	Do you advise parents to use short course high dose inhaled steroids during an acute attack of wheeze?	Always Sometimes Never		
1i	What percentage of PVW children do you start oral montelukast?			

2. In the management of children who wheeze with viral infection and with other triggers (e.g.: exercise, allergens etc):

	Management of acute wheezy episode			
2a	What percentage of children with PVW do you start oral steroids?			
2b	Usual dose of oral steroids	1mg/kg ☐	2mg/kg ☐	Other ☐
2c	Usual duration of oral steroids	1day ☐	3days ☐	5days ☐
2d	What percentage of children with PVW do you start oral montelukast?			
2e	First choice bronchodilators.	Salbutamol ☐	Atrovent ☐	
2f	Choice of initial delivery device.	Nebuliser ☐	Inhaler with spacer ☐	
	Clinic (Out patient) long-term management			
2g	What percentage of PVW children do you start inhaled steroids?			
2h	Do you advise parents to use short course high dose inhaled steroids during an acute attack of wheeze?	Always Sometimes Never		
2i	What percentage of PVW children do you start oral montelukast?			

Appendix 3: Invitation Letter

Date:

To:

Dear,

Re: Efficacy of a short course or oral steroids for hospitalised preschool children with viral induced wheeze; a randomised double blind placebo controlled trial.

A research study is being carried out at the Leicester Royal Infirmary/Queens Medical Centre Nottingham /City Hospital Nottingham by Dr J Grigg /Prof TJ Stephenson/Dr A Smyth.

The study has been designed to examine the effect of a short course of oral steroids for hospitalised preschool children with viral wheeze. Patients are being asked to answer questions about symptoms on discharge.

As you are currently being treated, your responses would be very valuable. It is hoped that the results of this study will help in the management of hospitalised preschool children with viral wheeze.

If you would like to take part in this study, details of which are given on the information leaflet enclosed, please complete the session below and return it to doctor/nurse. I would like to thank you for taking time to read this letter. If you have any queries, please feel free to contact me on the telephone number below.

Yours sincerely,

Dr Jonathan Grigg,
Department of child health.
Telephone No: 0116 252 5810.

- I am interested in taking part in the above study.

- I understand that I am under no obligation to take part in the study.

Name: …….

Address: ……
……
……
Telephone No: ……..

Date: ……..

Appendix 4: Parent Information Leaflet

Title of Study: Efficacy of a short course of oral steroids for hospitalised preschool children with viral-induced wheeze; a randomised double-blind placebo-controlled trial.

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

We are carrying out a study to find out whether a short course of oral steroids are helpful in treating wheezing attacks in preschool children.

Who is organising and funding the research?

The study is being organised by Dr Jonathan Grigg, senior lecturer at the University of Leicester, and honorary consultant. The research is funded by Asthma UK, the largest UK charity funding asthma research.

What is the purpose of this study?

We wish to find out whether a short course of oral steroids are helpful in reducing the severity of wheeze that is triggered by colds in preschool children. We have looked at this question in attacks of viral-triggered wheeze where parents have started oral steroids at home, and have found that they were not effective. We now want to look at this in children with more severe wheeze. Oral steroids are widely used to treat wheezing in school age children with allergic asthma. One reason why they may not be effective in the preschool age group is that most

young children do not have "allergic" asthma, but a condition which they grow out of by 6 years of age.

Why has my child been chosen?

We would like your child to take part because he or she has been judged by a hospital paediatrician has having a severe attack of wheeze that has been triggered by a cold.

Does my child have to take part? What happens if I do not wish my child to take part in this study or wish to withdraw him/her from the study?

It is up to you to decide whether or not to let your child take part. If you do decide to let your child take part you will be given this information sheet to keep and be asked to sign a consent form. If you let your child take part you are still free to withdraw your child at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care your child receives.

What will be involved if my child takes part in the study?

Your child with receive the normal inhaled doses of airway opening medication (salbutamol), and will also be given either oral prednisolone medication or dummy medication. The medication will be given once a day for 5 days. It will be provided inside a capsule, which can be opened. Just before giving the dose, the powder from the capsule can be added to a small amount of fruit drink. A doctor will assess the severity of wheeze using a score chart on admission to the ward and 4, 12 and 24 hours later (if he or she is still in hospital). The doctor will not know whether prednisolone or dummy medication has been given. We will record the length of stay in hospital, and ask you to fill out a diary card of your child's chest symptoms for a total of 7 days. A telephone follow up at 1 and 4 weeks post discharge will be carried out

for asking questions about disruptions to parental work, readmission to hospital and re attendance to GP.

Are there any risks?

There are no significant risks of either prednisolone or the dummy medication. A short course of oral steroids will not cause the effects on growth or ability to fight infection that can happen with long term use.

What is the drug or procedure that is being tested?

We are testing the use of oral prednisolone. This is a steroid that damps down abnormal activity of cells in the lung, and is very useful in treating allergic asthma.

What are the possible benefits of taking part?

Participation in this trial will give a definite answer whether oral steroids are useful or not useful in treating viral-triggered wheeze in preschool children. Either answer will have major implications for guidelines both in the UK and around the world. If they do produce some benefit- then we will recommend that all children with severe wheeze should receive this therapy. if they are ineffective will have to perform trials of alternatives. At the moment the only medication that has been shown to work is inhaled airway opening medications.

What happens when the research study stops?

Long-term treatment is not being provided as part of this study, so neither you nor anyone else will be disadvantaged when the study has finished. The results from all the participating children will be analysed once the research study stops. We will be sending a newsletter to all parents after we have analysed the results.

What if something goes wrong?

Medical research is covered for mishaps in the same way as receiving treatment in the NHS. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of the compensation arrangements, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Will my child's taking part in this study be kept confidential?

All information that is collected about your child and his/her family during the course of the research will be treated with the usual degree of confidentiality under the Data Protection Act. Any information about your child and the family that leaves the hospital will have his/her name and address removed so that neither the child nor the family can be recognised from it. However, we will inform your child's general practitioner that he/she is taking part in the study.

What will happen to the results of the research study?

The results of the study are likely to be published in a medical journal. It is unlikely that will occur before January 2008. No child who takes part in the research will be identified in any report/publication.

Will I receive out of pocket expenses if I allow my child to take part in this study?

There will be no expensed due to this study.

Contact for further information:

Chief Investigator: Dr Jonathan Grigg

Department of Child Health

University of Leicester

PO Box 65

Leicester LE2 7LX.

You may contact the investigator by:

Telephone – 0116 252 5810 (work)

Facsimile – 0116 252 3282

e-mail – jg33@le.ac.uk

Thank you for carefully reading this information. You will be given a copy of this Patient Information Sheet and a signed consent form to keep.

Patient Identification Number for this trial:

Appendix 5: Parent Consent Form

Title of Study: Efficacy of a short course of oral steroids for hospitalised preschool children with viral-induced wheeze; a randomised double-blind placebo-controlled trial.

Chief Investigator: Dr Jonathan Grigg
Department of Child Health
University of Leicester
PO Box 65
Leicester LE2 7LX.

You may contact the investigator by:
Telephone – 0116 252 5810 (work)
Facsimile – 0116 252 3282
e-mail – jg33@le.ac.uk.

Please initial box

1. I confirm that I have read and understand the parent information sheet, version 5, dated March 2006 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my child's participation is voluntary and that I am free to withdraw him/her at any time, without giving any reason, without any future medical care he/she may receive, or legal rights, being affected. ☐
3. I understand that my child will not be identified in any document relating to the trial. ☐
4. I agree for my child to take part in the above study. ☐
5. I agree for my child's case notes to be reviewed at a later date if necessary. ☐

_____	_____	_____
Name of Parent	Date	Signature
_____	_____	_____
(Child Signature if applicable)	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature
_____	_____	_____
Researcher	Date	Signature

1 for patient; 1 for researcher.

Appendix 6: GP Letter

Date

Dr
Address

Dear Dr,

Re: Your patient .....

Title of Study: Efficacy of a short course of oral steroids for hospitalised preschool children with viral-induced wheeze; a randomised double-blind placebo-controlled trial.

Your patient has recently agreed to participate in the above study, which is taking place at the Leicester Royal Infirmary. Details of the study are outlined in the enclosed information sheet.

If you require any further information please do not hesitate to contact me on (0116) 252 5810.

Yours sincerely,

Dr Jonathan Grigg,
Honorary Consultant Paediatrician,
Department of Child Health.

Appendix 7: Data Entry Sheets

Treatment of Wheeze in Children with Steroids -TWICS study

Participant number	

DATA SHEET

A. CHILD DETAILS

1	Bottle number (number on the trial medication bottle)			
2	Recruitment Date	day	month	year
3	Time of Randomisation, 24 hr clock			
4	Place of recruitment	Ward	A&E	Admissions unit

5. Attach a hospital sticker/write name,date of birth, gender, and address.

6	Main caregivers name	Surname First name
7	Telephone number Home: Mobile number: E-mail:	

B. MEASUREMENTS

8. TIME OF RANDOMISATION (Before giving trial medication)	Time

PRAM Score (Validated scale for wheeze) (Please circle or tick)

Signs				
Supra sternal retractions	Absent	Present		
Scalene muscle contraction	Absent	Present		
Air entry*	Normal	Decreased at bases	Widespread decrease	Absent/minimal
Wheezing*	Absent	Expiratory only	Inspiratory and expiratory	Audible without stethoscope/silent chest with minimal air entry
O2 saturation	≥ 95%	92%-94%	<92%	

*If asymmetry between right & left more severe side is rated

9. 4 HRS POST RANDOMISATION	Time

PRAM Score (Validated scale for wheeze) (Please circle or tick)

Signs				
Supra sternal retractions	Absent	Present		
Scalene muscle contraction	Absent	Present		
Air entry*	Normal	Decreased at bases	Widespread decrease	Absent/minimal
Wheezing*	Absent	Expiratory only	Inspiratory and expiratory	Audible without stethoscope/silent chest with minimal air entry
O2 saturation	≥ 95%	92%-94%	<92%	

*If asymmetry between right & left more severe side is rated

Fit for discharge after 4 hours Yes ☐ No ☐

Participant number	

10. 12 HRS POST RANDOMISATION	Time

PRAM Score (Validated scale for wheeze) (Please circle or tick)

Signs				
Supra sternal retractions	Absent	Present		
Scalene muscle contraction	Absent	Present		
Air entry*	Normal	Decreased at bases	Widespread decrease	Absent/minimal
Wheezing*	Absent	Expiratory only	Inspiratory and expiratory	Audible without stethoscope/silent chest with minimal air entry
O2 saturation	≥ 95%	92%-94%	<92%	

*If asymmetry between right & left more severe side is rated

11. 24 HRS POST RANDOMISATION	Time

PRAM Score (Validated scale for wheeze) (Please circle or tick)

Signs				
Supra sternal retractions	Absent	Present		
Scalene muscle contraction	Absent	Present		
Air entry*	Normal	Decreased at bases	Widespread decrease	Absent/minimal
Wheezing*	Absent	Expiratory only	Inspiratory and expiratory	Audible without stethoscope/silent chest with minimal air entry
O2 saturation	≥ 95%	92%-94%	<92%	

*If asymmetry between right & left more severe side is rated

DISCHARGE DETAILS

12	Date child fit for discharge	day	month	year
13	Time child fit for discharge (in 24hrclock)			
14	Date child was discharged	day	month	year
15	Time child discharged (in 24hrclock)			

	Time of rand	4hours	12hours	24hours
Temperature				
Heart rate				
Respiratory rate				

GP name, address & telephone no:

Treatment of Wheeze in Children with Steroids
-TWICS study
Parental history sheet

Participant number	

C. HISTORY SHEET (To be filled by Parent)

16. Present episode of wheeze

16a	When did your child develop symptoms of a cold?	day	month	year	
16b	Did he/she have	Cold/runny nose	Yes	No	Don't know
		Fever	Yes	No	Don't know
		Sore throat /ear ache	Yes	No	Don't know
16c	When did he/she start wheezing?	day	month	year	

16d	Before this episode did your child had any episode of wheeze and or asthma?	Yes	No	Don't know

IF Yes Answer Q17 **IF** No Go to Q 18

17. Diagnosis and severity of wheeze and or asthma

17a	Has your child ever been diagnosed as having asthma by a doctor or a nurse?	Yes	No	Don't know
17b	When did you first notice your child's wheezing? (age in months)	_____	**OR**	Don't know
17c	Does your child cough or wheeze apart from a cold?	Yes	No	Don't know

17d	How many attacks of cough or wheeze <u>lasting more than 2 days</u> has your child had in the last 12 months?	_____	**OR**	Don't know
17e	Has your child had any courses of steroid tablets (prednisolone) during the last 12 months? If so, how many courses of steroid tablets (prednisolone) has your child had during the last 12 months?	Yes _____	No **OR**	Don't know Don't know
17f	How many times has you child been admitted to hospital for wheeze before this attack?	_____	**OR**	Don't know
17g	How many times has your child been seen in A&E but not admitted to ward for wheezing, before this attack?	_____	**OR**	Don't know
17h	How many times has your child been seen in your G.P surgery for wheeze, before this attack?	_____	**OR**	Don't know

18. History of allergy

18a	Does your child have doctor diagnosed eczema	No	Past history (Yes, but it is now resolved)	Active eczema (Yes, and it is still there)	Don't know
18b	Does your child have doctor diagnosed hay fever	No	Past history (Yes, but it is now resolved)	Active hay fever (Yes, and it is still there)	Don't know
18c	Does your child have doctor-diagnosed food allergy?	No	Past history (Yes, but it is now resolved)	Active food allergy (Yes, and it is still there)	Don't know
18d	Are there any smokers in the household?	No	Yes	Don't know	
18e	History of parental asthma	No	Yes	Don't know	
18f	History of maternal asthma	No	Yes	Don't know	
18g	Did your child have bronchiolitis as an infant?	No	Yes	Don't know	

Participant number	

D. TREATMENT AT HOME

19	Is your child on any treatment for wheeze/ asthma at home?	Yes	No	Don't know

Regular treatment

20	Medication	Mode of delivery (Please circle)	PRN/Total daily dose	Medication	Mode of del	PRN/Total daily dose
	Salbutamol (Ventolin)	Oral/Inhaler/Nebuliser		Eformoterol (Oxis)	Inhaler	
	Terbutaline (Bricarnyl)	Inhaler/Nebuliser		Montelukast (Singulair)	Oral	
	Beclomethasone (Becotide)	Inhaler/Nebuliser		Theophylline (Slo-phyllin)	Oral	
	Budesonide (Pulmicort)	Inhaler/Nebuliser		Atrovent (Ipratr brom)	Inhaler	
	Fluticasone (Flixotide)	Inhaler		Oral steroid	Oral	
	Salmeterol (Serevent)	Inhaler				

21. Additional treatment given in the last week (week prior to randomisation)

21a	Has the child been started on any new treatment in the last 1 week				Yes No Don't know		
21b	If yes, the new treatment started in the last week				Mode of delivery		
	Bronchodilator (Short acting)	Salbutamol (Ventolin)	Terbutaline (Bricarnyl)	Atrovent (Ipratro B)	Inhaler	Nebuliser	Oral
	Steroid	Beclomethasone (Becotide)	Budesonide (Pulmicort)	Fluticasone (Flixotide)	Inhaler	Nebuliser	
	Bronchodilator (Long acting)	Salmeterol (Serevent)	Eformoterol (Oxis)		Inhaler	Nebuliser	
	Other	Montelukast (Singulair)	Theophylline (Slo-phyllin)		Oral		
21c	Increased dose of existing treatment in the last 1 week				Yes No Don't know		
21d	Oral antibiotics in the last 1 week				Yes No Don't know		

21e	Did he/she receive steroids before coming to hospital	Yes No Don't know
21f	How many doses of steroids did he/she have before coming to hospital	_____ **OR** Don't know
21g	How long ago did he/she receive the last dose of oral prednisolone?	(hours) _____ **OR** Don't know

E. TREATMENT IN HOSPITAL

22	Medication	Strength	Total no: of doses/ nebulisers	Medication	Strength	Total no: of doses/ nebulisers
	Salbutamol inhaler (Ventolin)			Budesonide (Pulmicort)		
	Salbutamol nebuliser (Ventolin)			Fluticasone (Flixotide)		
	Atrovent nebuliser (Ipratrop Bromide)			Salmeterol (Serevent)		
	Atrovent inhaler (Ipratrop Bromide)			Eformoterol (Oxis)		
	Terbutaline inhaler (Bricarnyl)			Montelukast (Singulair)		
	Beclomethasone (Becotide)			Theophylline (Slo-phyllin)		
	I/V hydrocortisone	Yes	No	Oxygen	Yes	No
	I/V terbutaline	Yes	No	I/V fluids	Yes	No
	I/V salbutamol	Yes	No	Antibiotics	Yes	No
	I/v aminophylline	Yes	No			

Participant number	

F. 1-WEEK TELEPHONE FOLLOW UP

23. Common side effect questionnaire

	Did you notice any of the following in the past 5 days			**If yes where they present before starting the trial medication**	**If yes where the symptoms present more than 4 hours after the last dose of salbutamol**
	Changes in appetite	Yes	No	Yes/No	Yes/No
	Tantrums	Yes	No	Yes/No	Yes/No
	Sleeplessness	Yes	No	Yes/No	Yes/No
	Hyperactivity	Yes	No	Yes/No	Yes/No
	Anxiety	Yes	No	Yes/No	Yes/No
	Aggressive behaviour	Yes	No	Yes/No	Yes/No

	Any other side effect noticed	

G. 4- WEEK TELEPHONE FOLLOW UP

24. Cost evaluation

24a	**After discharge from hospital, following initial admission for wheezing (breathing problems), have you had any (for viral wheeze)**			If Yes how many times
	GP (family doctor) consultation at GP surgery	Yes	No	
	GP (family doctor) home visit	Yes	No	
	Visit to practise nurse at GP surgery	Yes	No	
	A&E visit	Yes	No	
	Re-admission to hospital	Yes	No	
	New OP (outpatient) review	Yes	No	
	Ward review	Yes	No	

25	**Journeys made in the last 4 weeks for viral wheezing (breathing problems) (excluding the initial admission)**	No:	Mode of travel (Please circle)				One way cost or mileage for 1 journey	Time taken for each visit
			Car	Bus	Taxi	Other		
			Car	Bus	Taxi	Other		
			Car	Bus	Taxi	Other		
			Car	Bus	Taxi	Other		
	To hospital		Car	Bus	Taxi	Other		
			Car	Bus	Taxi	Other		
			Car	Bus	Taxi	Other		
			Car	Bus	Taxi	Other		
			Car	Bus	Taxi	Other		
	To GP surgery		Car	Bus	Taxi	Other		
26	**In the last 4 weeks total cost of providing a carer to mind an unwell child with viral wheeze (breathing problem), or look after other dependents when parents accompanied the child**							
27a	**In the last 4 weeks has any one taken time off work, to care for unwell child with viral wheeze (breathing problem)**						Yes	No
27b	If yes gender of the person	Male		Female			Both	
27c	Total duration of time taken off by each person							

28	Total no: of hospital admissions for viral wheeze 4 weeks following discharge	
29	Total no: of medical contacts for viral wheeze 4 week following discharge (excluding hospital admissions)	
30	Have there been additional cost due to your child's illness	Yes No Don't know
31	If yes can you give an estimate	
32	How many days after discharge were your child well enough to go to school/back to normal self?	

TWICS study

33. SYMPTOM DIARY FOLLOW-UP

	Date discharged			
	Trial medication number			
	Date symptom diary received			

Day of episode		1	2	3	4	5	6	7
Day time score								
Night time score								
GP visit (Yes/No)								
Hospital visits (Yes/No)								
Name of inhaler	Dose	Total number of puff given each day						
a)								
b)								
c)								
d)								
Name of nebuliser	Dose	Total number of doses each day						
a)								
b)								
Did you feel trial medication was		Helpful		Did not help			Don't know	

Appendix 8: Symptom Diary

Day of episode (Post discharge)	**1**	**2**	**3**	**4**	**5**	**6**	**7**
1. My child's wheeze or cough last night							
I did not hear my child wheezing or coughing last night							
I heard my child wheezing or coughing but he/she did not wake up							
My child woke up once because of wheezing or coughing but no help required							
My child woke up more than once because of wheezing or coughing or needed help.							
2. My child's wheeze or cough today							
My child had no wheeze or cough							
My child was wheezing or coughing but not bothered at all							
My child was wheezing or coughing but bothered only a little							
My child was wheezing or coughing and bothered quite a lot							
3. Today my child visited the GP or GP was called							
4. Today my child was taken to hospital because of wheezing							
5. Name of inhaler Dose	Write in the boxes the total number of puffs you gave your child						
a)							
b)							
c)							
d)							
6. Name of nebuliser Dose	Write in the boxes the total number of doses you gave your child						
a)							
b)							

Appendix 9: Flow charts

Treatment of Wheeze in Children with Steroids -TWICS study

Before discussing consent with the parents ensure the child fulfils the entry and exclusion criteria listed below.

ENTRY CRITERIA

1. Children aged 10 months to 60 months (5 years 0 months).

2. Preceding history of a viral illness with upper respiratory tract symptoms/signs associated with an acute episode of physician diagnosed wheeze (Pre school viral wheeze).

EXCLUSION CRITERIA

1. Children less than 10 months and more than 60 months.
2. Fluid resuscitation (more than or equal to 20 ml/kg).
3. Bacterial sepsis (eg: bacterial pneumonia, meningitis).
4. Cystic fibrosis, bronchiectasis and children with upper respiratory tract structural abnormality.
5. Children on home oxygen.
6. Diagnosis of immune deficiency.
7. Active chicken pox.
8. Children admitted for social reasons.

NB: Pre treatment with oral steroids or antibiotics is **not** an exclusion criterion**.** Asthma is **not** an exclusion criterion.

Yes ☐ Obtain consent and randomise.

No ☐ The child should not be entered into the trial but the details should be recorded on the Patient Not Enrolled Sheet.

Participant number	LR

Treatment of Wheeze in Children with Steroids -TWICS study

Everything you need is provided in this pack. Follow the explanatory note and checklist below

If the child is eligible for inclusion in the trial, from the TRIAL BOX get the next TRIAL PACK and give parent, invitation letter and parent information leaflet.

Explain to parent that there is no evidence at the moment, giving steroids help children with viral induced wheeze and hence we are doing this trial. Child's treatment won't change in any way. Only difference is child may get either steroid or placebo. Give them few minutes to make a decision.

Obtain WRITTEN CONSENT (Two copies, one for parent and one for researcher). Keep the consent form back in the trial pack.

Give PARENTS, HISTORY SHEET (Pink form) & SYMPTOM DIARY with FREE POST ENVELOPE to complete and collect the history sheet (Keep this in the trial pack). Parents to send back the symptom diary after filling it for 7 days after discharge.

Give child age appropriate trial medication. DOSE: 10 Mg (10m-24m) OR 20 Mg (25m-60m) ONCE DAILY FOR 5 DAYS. Trial medication is kept in admissions unit. Each bottle contains 5 capsules of either 10 mg or 20 mg. In the drug sheet write Trial medication (viral wheeze study)…. Mg once daily for 5 days. If the child is admitted send the bottle with the child to the ward. Child can have inhalers and nebulisers as usual, but don't give separate oral prednisolone. Once randomised, child should stay in hospital for at least 4 hours post randomisation till second set of observations are obtained.

Fill in variables 1-9 in the Data collection sheet (Yellow form) and patient obs on page 4 of the data collection sheet. Please make sure parents phone number is documented for follow up call.

Leave the completed forms in the trial pack and leave this in the child's notes. Please make sure you (or hand over) obtain second, third and fourth set of observations at 4, 12 and 24 hrs post randomisation respectively (if admitted).

CHECKLIST

PARENT		DOCTOR	
TWO consent forms signed.		Complete variables 1-9 on data sheet & observations on page 4 of data sheet.	
Completed parent history sheet.		Handover to complete 4hr, 12hr & 24hr PRAM score & observations.	
Symptom diary with free post envelope given.		Keep one copy of consent form, completed parent history sheet & data sheet back in trial pack and keep in child's notes.	

Treatment of Wheeze in Children with Steroids -TWICS study

PATIENT NOT ENROLLED SHEET

Please record the details of any child between 10 months and 60 months, admitted with viral wheeze (definition- preceding history of a viral illness with upper respiratory tract symptoms/signs associated with an acute episode of physician diagnosed wheeze) but not included into the trial, the reason and triage observation.

Age		**Gender**	Male	Female

Reason tick more than 1 if applicable

1	**Exclusion criteria met**	
	Fluid resuscitation (more than or equal to 20 ml/kg)	
	Bacterial Sepsis (eg: bacterial pneumonia, meningitis)	
	Cystic fibrosis, bronchiectasis	
	Children on home oxygen	
	Diagnosis of immune deficiency	
	Active chicken pox	
	Children admitted for social reasons	
2	**Not approached for consent**	
3	**Declined to take part**	
4	**Other - specify**	

5. First recorded observations

Heart rate		Temperature	
Respiratory rate		Oxygen saturation	

Participant number	LR

Treatment of Wheeze in Children with Steroids -TWICS study

Recruitment Checklist

Name:	
DOB:	
Participant number:	LR
Bottle (Trial medication) no:	

Date recruited:

Invitation letter given		Symptom diary returned	
Information leaflet given		1 week follow up telephone call	
Consent form signed		GP letter send	
Symptom diary given to parents		4 week follow up telephone call	
Data sheet information completed			

Data entry checklist

Data base completed	Yes No

Child details		Symptom diary	
History sheet		1 week telephone follow up	
Measurements		4 week telephone follow up	
Treatment at home			
Treatment in hospital			

Treatment of Wheeze in Children with Steroids -TWICS study

TRIAL LOG

LR No:	Bottle No (Number on the trial medication bottle)	Name	D.O.B	Hosp number

Treatment of Wheeze in Children with Steroids -TWICS study

INCLUSION CRITERIA

Children aged 10 months to 60 months

Preceding history of a viral illness with upper respiratory tract symptoms/signs associated with an acute episode of physician diagnosed wheeze.

Is the child eligible for inclusion in the trial

EXCLUSION CRITERIA

Fluid resuscitation more than or equal to 20 ml/kg.
Bacterial sepsis (bacterial pneumonia, meningitis)
Cystic fibrosis, bronchiectasis.
Children on home oxygen
Diagnosis of immune deficiency
Active chicken pox
Children admitted for social reasons.

NB: Pre treatment with oral steroids or antibiotics is not an exclusion criteria
Asthma is not an exclusion criteria.

Give parent and child if appropriate, invitation letter and parent information leaflet

Obtain written consent

Give child the trial medication
Give parents history sheet and symptom diary and collect the completed history sheet

Once randomised child should stay in hospital at least 4 hours post randomisation till second set of observations are obtained
Fill in variables 1-9 in the Data collection sheet
Please make sure parents phone number is documented to make the follow up call

Finally leave the completed forms in the plastic folder in the child's notes.

Appendix 10: Trial drug label

FOR CLINICAL TRIAL USE ONLY
Investigator: Dr J Grigg
Oral steroids for pre-school viral wheeze

(5) Prednisolone 10 mg capsules or placebo capsules

ONE capsule to be given daily
Give with or after food
Store in a cool dry place

Patient number:

Patient name:

Date dispensed:

Trial site:

Batch no:

Do not use after:

KEEP OUT OF THE REACH OF CHILDREN

Prepared by: Nova Laboratories Ltd, Martin House, Gloucester Crescent, Wigston LE18 4YL.
Tel: 0116 2230100

REFERENCES

1. Henderson J, Granell R, Sterne J. The search for new asthma phenotypes. Arch Dis Child 2009;94(5):333-336.

2. Saglani S, Bush A. Asthma in preschool children: the next challenge. Curr Opin Allergy Clin Immunol 2009;9(2):141-145.

3. Spycher BD, Silverman M, Barben J et al. A disease model for wheezing disorders in preschool children based on clinicians' perceptions. PLoS One 2009;4(12):e8533.

4. Spycher BD, Silverman M, Kuehni CE. Phenotypes of childhood asthma: are they real? Clin Exp Allergy 2010;40(8):1130-1141.

5. Bacharier LB, Phillips BR, Bloomberg GR et al. Severe intermittent wheezing in preschool children: a distinct phenotype. J Allergy Clin Immunol 2007;119(3):604-610.

6. Bush A. Coughs and wheezes spread diseases: but what about the environment? Thorax 2006;61(5):367-368.

7. Kurukulaaratchy RJ, Fenn MH, Waterhouse LM, Matthews SM, Holgate ST, Arshad SH. Characterization of wheezing phenotypes in the first 10 years of life. Clin Exp Allergy 2003;33(5):573-578.

8. La GS, Gagliardo R, Mirabella F et al. Clinical and biological heterogeneity in children with moderate asthma. Am J Respir Crit Care Med 2003;167(11):1490-1495.

9. O'Donnell RA, Frew AJ. Is there more than one inflammatory phenotype in asthma? Thorax 2002;57(7):566-568.

10. Kay AB. Allergy and allergic diseases. First of two parts. N Engl J Med 2001;344(1):30-37.

11. Larche M, Robinson DS, Kay AB. The role of T lymphocytes in the pathogenesis of asthma. J Allergy Clin Immunol 2003;111(3):450-463.

12. Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD. Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. N Engl J Med 1991;325(15):1067-1071.

13. Grigg, Silverman M. Wheezing disorders in young children: one disease or several phenotypes? European Respiratory Monograph. 2006:153-169.

14. Kuehni CE, Davis A, Brooke AM, Silverman M. Are all wheezing disorders in very young (preschool) children increasing in prevalence? Lancet 2001;357(9271):1821-1825.

15. Maclennan C, Hutchinson P, Holdsworth S, Bardin PG, Freezer NJ. Airway inflammation in asymptomatic children with episodic wheeze. Pediatr Pulmonol 2006;41(6):577-583.

16. Mertsola J, Ziegler T, Ruuskanen O, Vanto T, Koivikko A, Halonen P. Recurrent wheezy bronchitis and viral respiratory infections. Arch Dis Child 1991;66(1):124-129.

17. Stevenson EC, Turner G, Heaney LG et al. Bronchoalveolar lavage findings suggest two different forms of childhood asthma. Clin Exp Allergy 1997;27(9):1027-1035.

18. Allander T, Jartti T, Gupta S et al. Human bocavirus and acute wheezing in children. Clin Infect Dis 2007;44(7):904-910.

19. Silverman M, Wang M, Hunter G, Taub N. Episodic viral wheeze in preschool children: effect of topical nasal corticosteroid prophylaxis. Thorax 2003;58(5):431-434.

20. Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. N Engl J Med 1990;323(8):502-507.

21. Sporik R, Holgate ST, Cogswell JJ. Natural history of asthma in childhood--a birth cohort study. Arch Dis Child 1991;66(9):1050-1053.

22. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995;332(3):133-138.

23. Davies G, Paton JY, Beaton SJ, Young D, Lenney W. Children admitted with acute wheeze/asthma during November 1998-2005: a national UK audit. Arch Dis Child 2008;93(11):952-958.

24. Caudri D, Wijga A, CM AS et al. Predicting the long-term prognosis of children with symptoms suggestive of asthma at preschool age. J Allergy Clin Immunol 2009;124(5):903-910.

25. Papadopoulos NG, Kalobatsou A. Respiratory viruses in childhood asthma. Curr Opin Allergy Clin Immunol 2007;7(1):91-95.

26. Lemanske RF, Jr., Jackson DJ, Gangnon RE et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. J Allergy Clin Immunol 2005;116(3):571-577.

27. Stein RT, Sherrill D, Morgan WJ et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet 1999;354(9178):541-545.

28. Bont L, Aalderen WM, Kimpen JL. Long-term consequences of respiratory syncytial virus (RSV) bronchiolitis. Paediatr Respir Rev 2000;1(3):221-227.

29. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. Am J Respir Crit Care Med 2000;161(5):1501-1507.

30. Thomsen SF, van der Sluis S, Stensballe LG et al. Exploring the association between severe respiratory syncytial virus infection and asthma: a registry-based twin study. Am J Respir Crit Care Med 2009;179(12):1091-1097.

31. Bradley JP, Bacharier LB, Bonfiglio J et al. Severity of respiratory syncytial virus bronchiolitis is affected by cigarette smoke exposure and atopy. Pediatrics 2005;115(1):e7-14.

32. Hyvarinen MK, Kotaniemi-Syrjanen A, Reijonen TM, Korhonen K, Korppi MO. Teenage asthma after severe early childhood wheezing: an 11-year prospective follow-up. Pediatr Pulmonol 2005;40(4):316-323.

33. Horn SD, Smout RJ. Effect of prematurity on respiratory syncytial virus hospital resource use and outcomes. J Pediatr 2003;143(5 Suppl):S133-S141.

34. Lannero E, Wickman M, Pershagen G, Nordvall L. Maternal smoking during pregnancy increases the risk of recurrent wheezing during the first years of life (BAMSE). Respir Res 2006;7:3.

35. Rylander E, Eriksson M, Freyschuss U. Risk factors for occasional and recurrent wheezing after RSV infection in infancy. Acta Paediatr Scand 1988;77(5):711-715.

36. Mertsola J, Ziegler T, Ruuskanen O, Vanto T, Koivikko A, Halonen P. Recurrent wheezy bronchitis and viral respiratory infections. Arch Dis Child 1991;66(1):124-129.

37. Singh AM, Moore PE, Gern JE, Lemanske RF, Jr., Hartert TV. Bronchiolitis to asthma: a review and call for studies of gene-virus interactions in asthma causation. Am J Respir Crit Care Med 2007;175(2):108-119.

38. Kusel MM, de Klerk NH, Kebadze T et al. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. J Allergy Clin Immunol 2007;119(5):1105-1110.

39. Jackson DJ, Gangnon RE, Evans MD et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. Am J Respir Crit Care Med 2008;178(7):667-672.

40. Devulapalli CS, Carlsen KC, Haland G et al. Severity of obstructive airways disease by age 2 years predicts asthma at 10 years of age. Thorax 2008;63(1):8-13.

41. Hederos CA, Janson S, Andersson H, Hedlin G. Chest X-ray investigation in newly discovered asthma. Pediatr Allergy Immunol 2004;15(2):163-165.

42. Hofhuis W, Van Der Wiel EC, Tiddens HA et al. Bronchodilation in infants with malacia or recurrent wheeze. Arch Dis Child 2003;88(3):246-249.

43. Neve V, Edme JL, Devos P et al. Spirometry in 3-5-year-old children with asthma. Pediatr Pulmonol 2006;41(8):735-743.

44. Saito J, Harris WT, Gelfond J et al. Physiologic, bronchoscopic, and bronchoalveolar lavage fluid findings in young children with recurrent wheeze and cough. Pediatr Pulmonol 2006;41(8):709-719.

45. Young S, Arnott J, O'Keeffe PT, Le Souef PN, Landau LI. The association between early life lung function and wheezing during the first 2 yrs of life. Eur Respir J 2000;15(1):151-157.

46. Dundas I, Chan EY, Bridge PD, McKenzie SA. Diagnostic accuracy of bronchodilator responsiveness in wheezy children. Thorax 2005;60(1):13-16.

47. Nielsen KG, Bisgaard H. Discriminative capacity of bronchodilator response measured with three different lung function techniques in asthmatic and healthy children aged 2 to 5 years. Am J Respir Crit Care Med 2001;164(4):554-559.

48. Kharitonov SA, Barnes PJ. Exhaled markers of pulmonary disease. Am J Respir Crit Care Med 2001;163(7):1693-1722.

49. Baraldi E, Dario C, Ongaro R et al. Exhaled nitric oxide concentrations during treatment of wheezing exacerbation in infants and young children. Am J Respir Crit Care Med 1999;159(4 Pt 1):1284-1288.

50. Crater SE, Peters EJ, Martin ML, Murphy AW, Platts-Mills TA. Expired nitric oxide and airway obstruction in asthma patients with an acute exacerbation. Am J Respir Crit Care Med 1999;159(3):806-811.

51. Kharitonov SA, Yates DH, Barnes PJ. Inhaled glucocorticoids decrease nitric oxide in exhaled air of asthmatic patients. Am J Respir Crit Care Med 1996;153(1):454-457.

52. Moeller A, Franklin P, Hall GL et al. Inhaled fluticasone dipropionate decreases levels of nitric oxide in recurrenty wheezy infants. Pediatr Pulmonol 2004;38(3):250-255.

53. Buchvald F, Baraldi E, Carraro S et al. Measurements of exhaled nitric oxide in healthy subjects age 4 to 17 years. J Allergy Clin Immunol 2005;115(6):1130-1136.

54. Park ES, Golding J, Carswell F, Stewart-Brown S. Preschool wheezing and prognosis at 10. Arch Dis Child 1986;61(7):642-646.

55. Brand P.L.P, Baraldi E, Bisgaard H, et.al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. Eur Respir J 2008;32:1096-1110.

56. Akinbami LJ, Schoendorf KC. Trends in childhood asthma: prevalence, health care utilization, and mortality. Pediatrics 2002;110(2 Pt 1):315-322.

57. Lougheed MD, Garvey N, Chapman KR et al. The Ontario Asthma Regional Variation Study: emergency department visit rates and the relation to hospitalization rates. Chest 2006;129(4):909-917.

58. Global Strategy for Asthma Management and Prevention 2007 (update). (Accessed August 28, 2010, at http://www.ginasthma.com). 2010.

59. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. Am J Respir Crit Care Med 2000;162(4 Pt 1):1403-1406.

60. Wald ER, Guerra N, Byers C. Frequency and severity of infections in day care: three-year follow-up. J Pediatr 1991;118(4 Pt 1):509-514.

61. Kuehni CE, Strippoli MP, Low N, Brooke AM, Silverman M. Wheeze and asthma prevalence and related health-service use in white and south Asian pre-schoolchildren in the United Kingdom. Clin Exp Allergy 2007;37(12):1738-1746.

62. Kuehni CE, Brooke AM, Silverman M. Prevalence of wheeze during childhood: retrospective and prospective assessment. Eur Respir J 2000;16(1):81-85.

63. Kuehni CE, Strippoli MP, Low N, Brooke AM, Silverman M. Wheeze and asthma prevalence and related health-service use in white and south Asian pre-schoolchildren in the United Kingdom. Clin Exp Allergy 2007;37(12):1738-1746.

64. Patel SP, Jarvelin MR, Little MP. Systematic review of worldwide variations of the prevalence of wheezing symptoms in children. Environmental Health 2008;7(57).

65. Stevens CA, Turner D, Kuehni CE, Couriel JM, Silverman M. The economic impact of preschool asthma and wheeze. Eur Respir J 2003;21(6):1000-1006.

66. Stevens CA, Turner D, Kuehni CE, Couriel JM, Silverman M. The economic impact of preschool asthma and wheeze. Eur Respir J 2003;21(6):1000-1006.

67. British guideline on the management of asthma. Thorax 2003;58 Suppl 1:i1-94.

68. Adams NP, Bestall JB, Jones PW. Inhaled beclomethasone versus placebo for chronic asthma. Cochrane Database Syst Rev 2000;(4):CD002738.

69. Adams NP, Bestall JC, Lasserson TJ, Jones PW. Inhaled fluticasone versus placebo for chronic asthma in adults and children. Cochrane Database Syst Rev 2005;(2):CD003135.

70. Wilson N, Sloper K, Silverman M. Effect of continuous treatment with topical corticosteroid on episodic viral wheeze in preschool children. Arch Dis Child 1995;72(4):317-320.

71. Connett G, Lenney W. Prevention of viral induced asthma attacks using inhaled budesonide. Arch Dis Child 1993;68(1):85-87.

72. Svedmyr J, Nyberg E, Thunqvist P, Asbrink-Nilsson E, Hedlin G. Prophylactic intermittent treatment with inhaled corticosteroids of asthma exacerbations due to airway infections in toddlers. Acta Paediatr 1999;88(1):42-47.

73. Wilson NM, Silverman M. Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home. Arch Dis Child 1990;65(4):407-410.

74. Ducharme FM, Lemire C, Noya FJ et al. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. N Engl J Med 2009;360(4):339-353.

75. Horowitz L, Zafrir O, Gilboa S, Berger I, Wolach B. Acute asthma. Single dose oral steroids in paediatric community clinics. Eur J Pediatr 1994;153(7):526-530.

76. Smith M, Iqbal S, Elliott TM, Everard M, Rowe BH. Corticosteroids for hospitalised children with acute asthma. Cochrane Database Syst Rev 2003;(2):CD002886.

77. Csonka P, Kaila M, Laippala P, Iso-Mustajarvi M, Vesikari T, Ashorn P. Oral prednisolone in the acute management of children age 6 to 35 months with viral

respiratory infection-induced lower airway disease: a randomized, placebo-controlled trial. J Pediatr 2003;143(6):725-730.

78. Oommen A, Lambert PC, Grigg J. Efficacy of a short course of parent-initiated oral prednisolone for viral wheeze in children aged 1-5 years: randomised controlled trial. Lancet 2003;362(9394):1433-1438.

79. Webb MS, Henry RL, Milner AD. Oral corticosteroids for wheezing attacks under 18 months. Arch Dis Child 1986;61(1):15-19.

80. Braunstahl GJ, Overbeek SE, KleinJan A, Prins JB, Hoogsteden HC, Fokkens WJ. Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. J Allergy Clin Immunol 2001;107(3):469-476.

81. Chavasse R, Seddon P, Bara A, McKean M. Short acting beta agonists for recurrent wheeze in children under 2 years of age. Cochrane Database Syst Rev 2002;(3):CD002873.

82. Everard ML, Bara A, Kurian M. Anti-cholinergic drugs for wheeze in children under the age of two years. Cochrane Database Syst Rev 2000;(2):CD001279.

83. McDonald NJ, Bara AI. Anticholinergic therapy for chronic asthma in children over two years of age. Cochrane Database Syst Rev 2003;(3):CD003535.

84. Bisgaard H, Nielsen KG. Bronchoprotection with a leukotriene receptor antagonist in asthmatic preschool children. Am J Respir Crit Care Med 2000;162(1):187-190.

85. Hakim F, Vilozni D, Adler A, Livnat G, Tal A, Bentur L. The effect of montelukast on bronchial hyperreactivity in preschool children. Chest 2007;131(1):180-186.

86. Knorr B, Franchi LM, Bisgaard H et al. Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. Pediatrics 2001;108(3):E48.

87. Straub DA, Minocchieri S, Moeller A, Hamacher J, Wildhaber JH. The effect of montelukast on exhaled nitric oxide and lung function in asthmatic children 2 to 5 years old. Chest 2005;127(2):509-514.

88. Szefler SJ, Baker JW, Uryniak T, Goldman M, Silkoff PE. Comparative study of budesonide inhalation suspension and montelukast in young children with mild persistent asthma. J Allergy Clin Immunol 2007;120(5):1043-1050.

89. Bisgaard H, Zielen S, Garcia-Garcia ML et al. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. Am J Respir Crit Care Med 2005;171(4):315-322.

90. Robertson CF, Price D, Henry R et al. Short-course montelukast for intermittent asthma in children: a randomized controlled trial. Am J Respir Crit Care Med 2007;175(4):323-329.

91. van der Wouden JC, Uijen JH, Bernsen RM, Tasche MJ, de Jongste JC, Ducharme F. Inhaled sodium cromoglycate for asthma in children. Cochrane Database Syst Rev 2008;(4):CD002173.

92. Tasche MJ, van der Wouden JC, Uijen JH et al. Randomised placebo-controlled trial of inhaled sodium cromoglycate in 1-4-year-old children with moderate asthma. Lancet 1997;350(9084):1060-1064.

93. Seddon P, Bara A, Ducharme FM, Lasserson TJ. Oral xanthines as maintenance treatment for asthma in children. Cochrane Database Syst Rev 2006;(1):CD002885.

94. Schwarzer G, Bassler D, Mitra A, Ducharme FM, Forster J. Ketotifen alone or as additional medication for long-term control of asthma and wheeze in children. Cochrane Database Syst Rev 2004;(1):CD001384.

95. Conner WT, Dolovich MB, Frame RA, Newhouse MT. Reliable salbutamol administration in 6- to 36-month-old children by means of a metered dose inhaler and Aerochamber with mask. Pediatr Pulmonol 1989;6(4):263-267.

96. Holmgren D, Bjure J, Engstrom I, Sixt R, Sten G, Wennergren G. Transcutaneous blood gas monitoring during salbutamol inhalations in young children with acute asthmatic symptoms. Pediatr Pulmonol 1992;14(2):75-79.

97. Kraemer R, Frey U, Sommer CW, Russi E. Short-term effect of albuterol, delivered via a new auxiliary device, in wheezy infants. Am Rev Respir Dis 1991;144(2):347-351.

98. Nielsen KG, Bisgaard H. Bronchodilation and bronchoprotection in asthmatic preschool children from formoterol administered by mechanically actuated dry-powder inhaler and spacer. Am J Respir Crit Care Med 2001;164(2):256-259.

99. Pool JB, Greenough A, Gleeson JG, Price JF. Inhaled bronchodilator treatment via the nebuhaler in young asthmatic patients. Arch Dis Child 1988;63(3):288-291.

100. Cates CJ, Crilly JA, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. Cochrane Database Syst Rev 2006;(2):CD000052.

101. Gibson PG, Wlodarczyk JH, Borgas T. Drug delivery in asthma: a comparison of spacers with a jet nebuliser. Aust N Z J Med 1995;25(4):324-329.

102. Mason N, Roberts N, Yard N, Partridge MR. Nebulisers or spacers for the administration of bronchodilators to those with asthma attending emergency departments? Respir Med 2008;102(7):993-998.

103. Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma. Cochrane Database Syst Rev 2000;(2):CD000195.

104. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. Cochrane Database Syst Rev 2001;(1):CD002178.

105. National Heart,Lung,and Blood Institute. Expert panel report 3:guidelines for the diagnosis and management of asthma:full report 2007.(Accessed August 28, 2010 at http://www.nhlbi.nih.gov/guidelines/asthma/.). 2010.

106. Jartti T, Lehtinen P, Vanto T et al. Evaluation of the efficacy of prednisolone in early wheezing induced by rhinovirus or respiratory syncytial virus. Pediatr Infect Dis J 2006;25(6):482-488.

107. Jartti T, Lehtinen P, Vanto T et al. Atopic characteristics of wheezing children and responses to prednisolone. Pediatr Pulmonol 2007;42(12):1125-1133.

108. Tal A, Levy N, Bearman JE. Methylprednisolone therapy for acute asthma in infants and toddlers: a controlled clinical trial. Pediatrics 1990;86(3):350-356.

109. Saglani S, Wilson N, Bush A. Should preschool wheezers ever be treated with inhaled corticosteroids? Semin Respir Crit Care Med 2007;28(3):272-285.

110. Wainwright C, Altamirano L, Cheney M et al. A multicenter, randomized, double-blind, controlled trial of nebulized epinephrine in infants with acute bronchiolitis. N Engl J Med 2003;349(1):27-35.

111. Stafler P. Dexamethasone for bronchiolitis. N Engl J Med 2007;357(16):1659-1660.

112. Chalut DS, Ducharme FM, Davis GM. The Preschool Respiratory Assessment Measure (PRAM): a responsive index of acute asthma severity. J Pediatr 2000;137(6):762-768.

113. Cunninghams Manual of Practical Anatomy: Volume 3. Head and Neck and Brain. 15 ed. Oxford Medical Publications; 2010.

114. Ducharme FM, Chalut D, Plotnick L et al. The Pediatric Respiratory Assessment Measure: a valid clinical score for assessing acute asthma severity from toddlers to teenagers. J Pediatr 2008;152(4):476-80, 480.

115. Santanello NC, Barber BL, Reiss TF, Friedman BS, Juniper EF, Zhang J. Measurement characteristics of two asthma symptom diary scales for use in clinical trials. Eur Respir J 1997;10(3):646-651.

116. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? Eur Respir J 1999;14(1):23-27.

117. Santanello NC, Davies G, Galant SP et al. Validation of an asthma symptom diary for interventional studies. Arch Dis Child 1999;80(5):414-420.

118. Malo JL, L'archeveque J, Trudeau C, d'Aquino C, Cartier A. Should we monitor peak expiratory flow rates or record symptoms with a simple diary in the management of asthma? J Allergy Clin Immunol 1993;91(3):702-709.

119. Falconer A, Oldman C, Helms P. Poor agreement between reported and recorded nocturnal cough in asthma. Pediatr Pulmonol 1993;15(4):209-211.

120. Ferguson AC. Persisting airway obstruction in asymptomatic children with asthma with normal peak expiratory flow rates. J Allergy Clin Immunol 1988;82(1):19-22.

121. Chang AB, Newman RG, Carlin JB, Phelan PD, Robertson CF. Subjective scoring of cough in children: parent-completed vs child-completed diary cards vs an objective method. Eur Respir J 1998;11(2):462-466.

122. Lara M, Duan N, Sherbourne C et al. Differences between child and parent reports of symptoms among Latino children with asthma. Pediatrics 1998;102(6):E68.

123. Braun-Fahrlander C, Gassner M, Grize L et al. Comparison of responses to an asthma symptom questionnaire (ISAAC core questions) completed by adolescents and their

parents. SCARPOL-Team. Swiss Study on Childhood Allergy and Respiratory Symptoms with respect to Air Pollution. Pediatr Pulmonol 1998;25(3):159-166.

124. Michel G, Silverman M, Strippoli MP et al. Parental understanding of wheeze and its impact on asthma prevalence estimates. Eur Respir J 2006;28(6):1124-1130.

125. Levy ML, Godfrey S, Irving CS et al. Wheeze detection: recordings vs. assessment of physician and parent. J Asthma 2004;41(8):845-853.

126. Elphick HE, Ritson S, Rodgers H, Everard ML. When a "wheeze" is not a wheeze: acoustic analysis of breath sounds in infants. Eur Respir J 2000;16(4):593-597.

127. Elphick HE, Sherlock P, Foxall G et al. Survey of respiratory sounds in infants. Arch Dis Child 2001;84(1):35-39.

128. Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by "wheeze"? Arch Dis Child 2000;82(4):327-332.

129. Cane RS, McKenzie SA. Parents' interpretations of children's respiratory symptoms on video. Arch Dis Child 2001;84(1):31-34.

130. Chowienczyk PJ, Parkin DH, Lawson CP, Cochrane GM. Do asthmatic patients correctly record home spirometry measurements? BMJ 1994;309(6969):1618.

131. Efron B, Tibshirani RJ. An introduction to the bootstrap. Boca Raton FL. Chapman & Hall/CRC Press; 1994.

132. Matricardi PM, Illi S, Gruber C et al. Wheezing in childhood: incidence, longitudinal patterns and factors predicting persistence. Eur Respir J 2008;32(3):585-592.

133. Weinberger M. Should corticosteroids be used for first time young wheezers? J Allergy Clin Immunol 2007;119:567-569.

134. Lehtinen P, Ruohola A, Vanto T, Vuorinen T, Ruuskanen O, Jartti T. Prednisolone reduces recurrent wheezing after a first wheezing episode associated with rhinovirus infection or eczema. J Allergy Clin Immunol 2007;119(3):570-575.

135. Sherrill DL, Stein R, Halonen M, Holberg CJ, Wright A, Martinez FD. Total serum IgE and its association with asthma symptoms and allergic sensitization among children. J Allergy Clin Immunol 1999;104(1):28-36.

136. Fox GF, Marsh MJ, Milner AD. Treatment of recurrent acute wheezing episodes in infancy with oral salbutamol and prednisolone. Eur J Pediatr 1996;155(6):512-516.

137. Altmann DG. Clinical trials. In: Altmann DG, editor. Practical Statistics for Medical Research. Chapman & Hall/CRC; 1991:325-361.