Oral prednisolone in preschool children with virus-associated wheeze: a prospective, randomised, double-blind, placebo-controlled trial

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Summary

Background Children of preschool age often have episodes of virus-associated wheeze, and research assessing efficacy of corticosteroids for paediatric wheeze exacerbations is inconclusive.

Methods This non-inferiority, randomised, double-blind, placebo-controlled trial was to compare the efficacy of placebo versus oral prednisolone in children aged 24–72 months presenting with virus-associated wheeze at the paediatric emergency department of Princess Margaret Hospital in Perth, WA, Australia. Eligible participants were randomly assigned (1:1) using a computer-generated random number program to receive placebo or prednisolone (1 mg/kg per day) for 3 days. The primary outcome was total length of stay in hospital until ready for discharge. Following an analysis to test the hypothesis that placebo is non-inferior to prednisolone, a post-hoc superiority analysis was done to test the hypothesis that prednisolone was superior to placebo. A non-inferiority margin of 10% was used to establish non-inferiority. Efficacy analyses were on a modified intention-to-treat basis, whereby patients were excluded from the final efficacy analysis if consent was withdrawn, two doses of study drug were vomited, or paperwork was lost. All participants were included in safety analyses. This study is registered with the Australian and New Zealand Clinical Trials Registry, number ACTRN12612000394842.

Findings Between June 11, 2012, and June 10, 2015, we screened 3727 patients for eligibility. 624 eligible patients were randomly assigned to treatment, and 605 patients were included in the modified intention-to-treat analysis (300 patients from the placebo group, 305 patients from the prednisolone group). The median length of stay until ready for discharge was longer in the placebo group (540 min [IQR 124–971]) than in the prednisolone group (370 min [121–709]); placebo was inferior to prednisolone. In the post-hoc superiority analysis of 605 patients, the unadjusted ratio of geometric mean for length of stay was 0·79 (95% CI 0·64–0·97; p=0·0227) for the prednisolone group relative to the placebo group. No serious adverse events were reported during the study or follow-up period. One child in the placebo group had a non-specific maculopapular rash, which resolved spontaneously. Two children (one from each group) were reported to be hyperactive during follow-up assessments.

Interpretation Oral prednisolone had a clear benefit over placebo at reducing the length of stay in children presenting to a paediatric emergency department with virus-associated wheeze and was well tolerated.

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Introduction

One in three children have an episode of wheeze before their third birthday, and the cumulative prevalence of wheeze is almost 50% at 6 years.[1,2] Detectable viruses are present in up to 88% of children of preschool age with wheezing episodes,[3] and these viruses are presumed to be the triggering factor to the wheezing episode.

Wheeze in children at preschool age follows a different clinical course to asthma in adolescents and adults,[4,5] with different observable pathophysiological mechanisms.[6–9] The beneficial role of corticosteroid administration in reducing the need for adults to seek hospital admission during asthma episodes has been shown,[10] but the evidence supporting corticosteroid use in paediatric wheeze exacerbations is less robust.[11] In particular, studies aimed at assessing the efficacy of corticosteroids on preschool children with wheeze have produced contradictory findings.[12–14] Panickar and colleagues,[14] having completed

the largest of these studies to date, found no positive effect of corticosteroids. Despite reservations[15] in the generalisable application of the findings by Panickar and colleagues, their conclusions have been adopted into guidelines for wheeze in this age group,[16,17] with corticosteroids no longer recommended as first-line therapy.

The objective of this study was to assess the efficacy of oral prednisolone in children presenting to a paediatric emergency department with suspected virus-associated wheeze.

Methods

Study design

This randomised, double-blind trial was done in the paediatric emergency department of Princess Margaret Hospital in Perth, WA, Australia. Presenting patients were randomly assigned to a 3-day course of either oral prednisolone or placebo once daily. Princess Margaret

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Research in context

Evidence before this study

We searched MEDLINE, Embase, and the Cochrane Library from inception until Aug 25, 2017, for any full reports of trials, systematic reviews, and meta-analyses using the terms "wheeze", "asthma", "glucocorticoid*", "prednisolone", "prednisone", and "dexamethasone". We limited the search to studies in human beings and children. We excluded studies in adults and studies in which the steroid was not delivered as an oral medication. Six studies were identified as relevant and sufficient quality (randomised control trials). The investigators of the most recent of these studies (in 2009) concluded that oral prednisolone was not superior to placebo in children of preschool age presenting to hospital with mild-to-moderate wheezing associated with a viral infection. This conclusion was in direct contradiction to findings of a previous study that led investigators to conclude that a 3-day course of oral prednisolone effectively reduced disease severity, length of hospital stay, and the duration of symptoms in children aged 6–35 months with virally induced respiratory distress. Both studies received criticism for the inclusion of patients who were probably presenting with bronchiolitis rather than virus-associated wheeze. The remaining studies did not limit their participant recruitment to preschool aged patients or were post-hoc analyses that were too underpowered for any meaningful interpretation.

Added value of this study

Oral prednisolone was beneficial compared with placebo in reducing the length of hospital stay in preschool aged children presenting with virus-associated wheeze. We ensured that all participants were presenting with virus-associated wheeze and not bronchiolitis by setting the lowest age limit to 2 years. We identified the specific trigger virus for the wheezing episode in almost two-thirds of participants, which has not been investigated or reported to date. This study also included patients presenting with more severe exacerbations of wheeze than previously studied, and our findings from subgroup analyses showed that oral corticosteroid was most effective in patients with features of severe wheeze or a history of asthma.

Implications of all the available evidence

Oral prednisolone should be administered early in the management of virus-associated wheeze in preschool aged children presenting to the emergency department. The greatest efficacy of prednisolone in virus-associated wheeze was seen in patients with features of severe wheeze or a history of asthma and appeared to be independent of the triggering virus type.

Hospital is the sole tertiary paediatric emergency department for WA, Australia, with an annual census of about 70 000 patients. The trial was originally designed and is reported as a non-inferiority trial to test the hypothesis that placebo is non-inferior to prednisolone. After the completion of data collection and before data analysis, the study's analysis plan was revised to include, following the completion of the analysis for the primary non-inferiority hypothesis, a post-hoc superiority analysis testing the hypothesis that prednisolone was superior to placebo. This change was made to: (1) ensure the reported results were in line with, and hence, directly comparable with the existing literature; (2) aid in the inclusion of this study's results in future meta-analyses; (3) provide effect sizes in a direction that facilitates a more intuitive interpretation for clinicians; and (4) aid in interpretation because the placebo intervention in this trial is not something that could feasibly be implemented as a treatment regimen within standard clinical practice. The study was approved by the institution's Child and Adolescent Health Service Human Research and Ethics Committee.

See **Online** for appendix

Patients

Eligible patients were children aged 24–72 months presenting to the paediatric emergency department with a clinical diagnosis of wheeze plus symptoms or signs of a viral upper respiratory tract infection. Predefined exclusion criteria were: presenting oxygen saturation less than 92% in room air, features of critical wheeze (silent chest on auscultation or exhaustion with or without cyanosis), clinical evidence of shock or bacterial sepsis, active varicella infection, high clinical suspicion of alternative diagnosis for wheeze (such as inhaled foreign body), previous intensive care unit admission with wheeze or asthma, premature birth (defined as <34 weeks' gestation), known cardiac or other respiratory disease, ongoing immunosuppressant therapy or immunodeficiency, upper respiratory tract structural abnormality, oral corticosteroid therapy within the preceding 14 days, known allergy to prednisolone, or previous enrolment in the current study. The paediatric emergency department staff screened all eligible children, and those who were confirmed as meeting criteria received bronchodilator therapy as per Princess Margaret Hospital guidelines (appendix). Written informed consent was obtained from the child's guardian.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to receive either prednisolone or placebo (formulated by the hospital manufacturing pharmacy and matched for volume, concentration, colour, smell, and taste). The study drugs were prepared into matching bottles, identified only by a four-digit study number. The randomisation schedule was prepared by the clinical pharmacist and was double-blind; computer-generated study numbers were assigned sequentially and randomisation carried out in blocks of six. The clinical pharmacist labelled all bottles with blinded study numbers and retained the randomisation code. Patients, guardians, doctors, the research team, and

biostatistician were all masked to group allocation through to the completion of statistical analysis.

Procedures

To assess the severity of the wheeze, a pulmonary score (ranging from 0 for no wheeze or very mild wheeze, to 9 for severe wheeze)[18] was calculated by the clinician at initial clinical assessment. Before receiving inhospital bronchodilator of six puffs of salbutamol (100 mg per metered dose; Ventolin, GlaxoSmithKline, Australia) via a small-volume spacer (Space Chamber Plus, Medical Developments International, Australia), data were collected for initial physiological parameters, symptom presence and duration, drugs received before admission to the paediatric emergency department, and family history of asthma or atopy. Guardians completed a questionnaire about the management of the wheeze episode before attendance at the paediatric emergency department, past wheezing and medical history, past therapies for wheeze, and childhood environment relating to breastfeeding and exposure to tobacco smoke. A nasal specimen was collected from each patient using a flocked swab, which was stored and tested via the standard hospital laboratory protocols for viral detection.[19] Patients were then randomly assigned to begin oral prednisolone (1 mg/kg) or placebo treatment once a day for 3 days.

Upon randomisation, the next numbered bottle of study drug was selected by the treating doctor, and the first dose of prednisolone (Redipred, Aspen Pharmacare Australia) or placebo was administered by a nurse. Subsequent doses were administered either by the guardian after discharge or, if admitted, by ward staff as prescribed to complete the 3-day course. If the patient vomited within 30 min of the first dose, administration was repeated. If vomiting recurred, the patient was withdrawn from the study, the vomitting was recorded as an adverse event, and further care for the patient was determined by the treating clinician.

All patients continued treatment as per hospital guidelines for wheeze, with the decision on further bronchodilator therapy made by the treating clinician. The response to therapy was assessed before the disposition decision of discharge home, admission to emergency short stay unit (ESSU), or direct admission to the inpatient ward. The ESSU is located within the paediatric emergency department and solely managed by paediatric emergency staff; many patients determined to be stable but not suitable for discharge within 4 h were admitted to the ESSU for up to 24 h.

A definite dose of corticosteroid was administered to the patient if the clinician admitting the patient to the inpatient ward deemed this necessary, and the patient remained in the intention-to-treat analysis and completed the follow-up data collection as planned. The continuation of the study drug was at the discretion of the inpatient clinician. Patients who were admitted were ready for discharge when their respiratory status had improved, as evidenced by no substantial wheeze with good air entry, tolerating 3-h bronchodilator therapy, and clinical observations within normal age-appropriate range. This was determined by study research assistants using the predetermined criteria on chart review. By contrast, the decision to discharge patients from the emergency department or ESSU was determined and recorded by the treating clinician in real time. Subsequent un-scheduled medical attendances or adverse clinical events were captured at follow-up via completion of a 7-day symptom diary and at a 10-day and 3-month phone call by masked research assistants.

Adverse events were monitored throughout the study. During follow-up phone calls, guardians were asked for the presence of vomiting or any other reasons (eg, rashes, behavioural changes) for not completing the study drug. An independent data and safety monitoring committee (DSMC) with no other role in the study reviewed any reported serious adverse events.

Outcomes

The dual primary outcomes of the study were originally specified as length of stay within the emergency depart-ment and the total length of stay within the hospital. These outcomes were initially defined to reflect global variation pertaining to the way patients are managed within emergency departments before transfer of the patient to inpatient services. During the recruitment phase of the study, the primary outcome of length of stay within the emergency department was determined as not reflective of the clinical condition and ongoing man-agement needs of the patients included in the study. Numerous non-clinical factors were identified, including capacity pressures and the administrative 4-h rule[20] that affected the length of stay in the emergency department and the use of ESSU to allow prolonged managed care in the emergency department until the need for inpatient care was determined. Given the limitations of the original primary outcome, it was revised to only total length of stay within the hospital until ready for discharge (both emergency department and inpatient, if applicable) to objectively reflect the clinical course of the study patients. The total length of stay was calculated as the difference (in minutes) between the time of study drug admini-stration and the predefined clinical state of ready for discharge. The actual length of stay was also examined but was deemed less accurate because it is affected by non-clinical factors such as the time of day the patient was ready to be discharged and delays in families arranging transport to their place of residence.

Secondary outcome measures relating to the first 7 days after hospital discharge included hospital or general practitioner re-attendance, hospital readmission, mean number and duration of salbutamol treatments given in hospital and during the first 7 days after discharge, mean duration of residual symptoms after discharge,
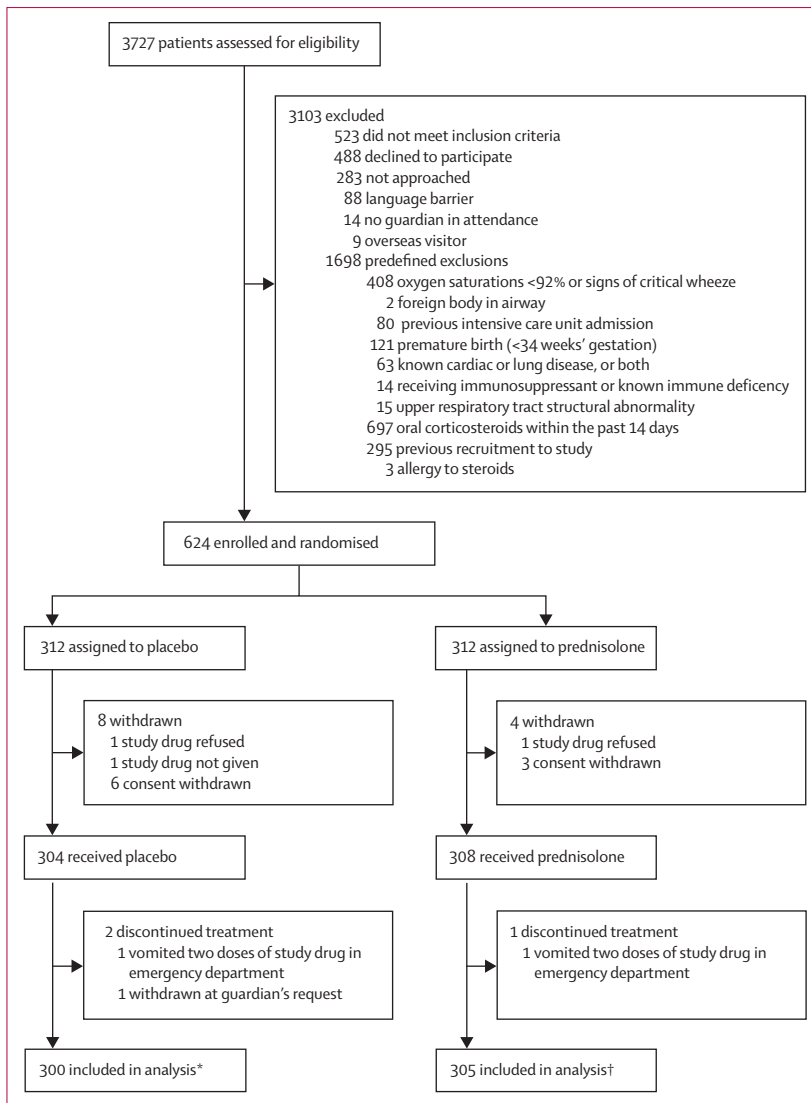
Figure 1: Trial profile
*Study paperwork was missing for two patients. †Study paperwork was missing for two patients.

and incidence of additional therapies introduced. Data relating to the longer-term effect of corticosteroid use were collected for the following secondary outcomes at 3 months after discharge: recurrence of wheeze; drugs regularly administered for wheeze; and number of medical attendances for wheeze. Virus identification data were collected for the influence of virus type on disease severity, symptom duration, wheeze recurrence, and effect of corticosteroid in wheeze in different virus types acutely.

Outcomes related to the enrolment emergency department attendance and those measured within the first 7 days after hospital discharge are presented fully here. The remaining secondary outcomes detailed above will be presented in subsequent manuscripts focusing on the longer-term effect of corticosteroids

and the role different virus types may have in this patient cohort.

Statistical analysis
The study was powered on the basis of the planned analysis of participants exceeding a 4-h stay within the paediatric emergency department. Assuming 45% of participants in the prednisolone group met this condition, the study required 304 participants per group to have sufficient (>80%) power to determine non-inferiority, with a non-inferiority margin of 10% and an α value of 0·05. An interim analysis was done by an independent biostatistician after the discharge of the 304th patient. The DSMC reviewed the results of this interim analysis and approved the continuation of the study. Categorical variables were compared between groups using a χ² test or Fisher's exact test; continuous variables were compared using Student's t test (parametric variables).

The analysis of length of stay until ready for discharge consisted of linear regression with length of stay log-transformed before analysis. The model coefficients, reported with 95% CI, are thus interpreted as the unadjusted or adjusted ratio of geometric means for the prednisolone group relative to the placebo group. As a deviation from the protocol, which pre-specified intention-to-treat analysis, we did a modfied intention-to-treat analysis whereby patients in the placebo and predniolone groups were not included in the final analysis because consent was withdrawn, two doses of study drug were vomited, or paperwork was lost. Potential confounders adjusted for in the analysis were defined a priori and included age, personal and family history of atopy, baseline pulmonary score, and presence of virus. A Kaplan-Meier survival plot was generated to graphically present length of stay by group.

As a post-hoc sensitivity analysis, to demonstrate the robustness of the observed results and aid in both decision making and hypothesis generation,[21] the primary outcome measure, length of stay until ready for discharge, was examined as three different derived dichotomous variables: (1) length of stay longer than 4 h to examine the effect of treatment on short-term hospital stays, in line with the administrative 4-h rule;[20] (2) length of stay longer than 7 h, as a reflection of the overall observed median length of stay; and (3) length of stay longer than 12 h, to represent a longer inhospital stay. In a prespecified subgroup analysis, data were stratified by wheeze severity as defined by the objective measured pulmonary score category (adapted from the institution's wheeze management guidelines; appendix). The pulmonary score, devised by Smith and colleagues,[18] provides a score relative to exacerbation severity and was an established adjunct to clinical assessment used in the paediatric emergency department before study com-mencement. All staff were competent in its use, and it was therefore chosen as a pragmatic severity scoring system for the study. The pulmonary score does not explicitly categorise

exacerbation severity specifically into mild, moderate, or severe. After an inspection of pulmonary score distribution, and on the basis of clinical insights into the definition of pulmonary score, a pulmonary score of less than 5 was used to classify a clinical presentation of wheeze as mild, a score of 5 as moderate, and a score of more than 5 as severe. Data were also stratified by viral antigen status (where data were available) and by history of asthma status. In post-hoc subgroup analyses, participants were stratified by use of salbutamol before arrival at the emergency department as a subjective marker of wheeze severity.

With the exception of the per-protocol analysis, dichotomous outcomes were analysed using log-binomial regression with effects expressed as a relative risk with 95% CI; the per-protocol analysis was completed using logistic regression with effects expressed as odds ratios with 95% CI.

All data manipulation and analysis were completed in R version 3.3.2. This study is registered with the Australian and New Zealand Clinical Trials Registry, number ACTRN12612000394842.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 11, 2012, and June 10, 2015, 3727 children were screened for study eligibility; of these, 523 did not meet the inclusion criteria, 488 declined to participate, and 1698 met the exclusion criteria (figure 1). 624 children were randomly assigned to receive placebo (n=312) or prednisolone (n=312). After consent withdrawals, treatment discontinuations, and misplaced study paperwork, data were available for the modified intention-to-treat analysis from 605 patients (300 patients in the placebo group and 305 patients in the prednisolone group).

The study groups were well balanced with no clinically significant differences between groups in baseline demographics, pulmonary score at presentation, personal or family history of atopy, or use of salbutamol before admission to the paediatric emergency department (table 1).

Analysis of the study's primary hypothesis showed that the placebo treatment was inferior to prednisolone (adjusted odds ratio for the length of stay until ready for discharge exceeding 4 h for participants on placebo relative to prednisolone 1·04, 95% CI 0·71–1·52; the upper bound of the 95% CI exceeds 1·1 thus crossing the 10% non-inferiority margin; appendix). The length of stay until ready for discharge for the placebo group was increased relative to the prednisolone group (unadjusted ratio of geometric mean 1·27, 95% CI 1·03–1·56; appendix). We found no difference between groups for the

distribution of disposition decisions (p=0·06). All participants who were directly discharged from the paediatric emergency department (99 in the placebo group vs 100 in the prednisolone group) had a length of stay shorter than 4 h with no difference in length of stay (median 83·0 min for placebo vs 79·0 min for prednisolone; p=0·16; appendix). Length of stay exceeded 4 h for 97% of the remaining 406 participants as they all received observation or treatment within either the ESSU or inpatient ward.

The results that follow all relate to the post-hoc superiority analysis; however, all results (including from the subgroup analysis) are available within the appendix as they pertain to the non-inferiority hypothesis.

The length of stay until ready for discharge was significantly reduced in the prednisolone group compared with the placebo group (the reciprocal of the above non-inferiority result) with the unadjusted ratio of geometric mean of 0·79 (95% CI; 0·64–0·97; p=0·0227) and showed little change after adjustment for confounders as planned a priori (table 2). This was evident despite the relatively short median length of stay in both placebo and prednisolone groups (table 2). The unadjusted ratio of geometric means was similar when length of stay was calculated using the ready for discharge and actual discharge length of stay (0·, 95% CI 0·63–0·97; p=0·0269). All remaining analyses continue to use length of stay until ready for discharge.

In the sensitivity analysis, we found no difference between groups in risk of discharge occurring within 4 h. However, patients in the prednisolone group had reduced risk of their length of stay exceeding either 7 h (adjusted relative risk [RR] 0·82, 95% CI 0·69–0·96; p=0·0166) or 12 h (0·67, 0·51–0·86; p=0·0018). Prednisolone seemed to be more efficacious than placebo as length of stay until

|	Placebo (n=300)	Prednisolone (n=305)
Age, months	41·3 (13·2)	41·2 (12·6)
Sex		
Female	91 (30%)	106 (35%)
Male	209 (70%)	199 (65%)
Current or previous smoker in home	95 (32%)	96 (32%)
Family history of asthma	180 (63%)	185 (62%)
Previous diagnosis of asthma in child	80 (27%)	65 (21%)
Previous use of steroids for wheeze management	82 (27%)	81 (27%)
Previous wheeze in child	211 (70%)	209 (69%)
Salbutamol pre PED attendance	215 (72%)	218 (72%)
Pulmonary score at admission	4·0 (1·6)	4·0 (1·4)
Pulmonary score category at admission		
<5 (mild)	166 (55%)	182 (60%)
5 (moderate)	83 (28%)	75 (25%)
>5 (severe)	51 (17%)	48 (16%)

Data are mean (SD) or n (%). PED=paediatric emergency department.

Table 1: Baseline characteristics

	Placebo (n=300)	Prednisolone (n=305)	Unadjusted model coefficient (95% CI)*	p value	Adjusted model coefficient (95% CI)†	p value
Primary outcome						
Length of stay, min	540 (124–971)	370 (121–709)	0·79 (0·64–0·97)	0·0227	0·80 (0·65–0·99)	0·0393
Sensitivity analysis						
Length of stay >4 h	196 (65%)	195 (64%)	0·98 (0·87–1·10)	0·72	1·01 (0·89–1·14)	0·89
Length of stay >7 h	170 (57%)	139 (46%)	0·80 (0·69–0·94)	0·0067	0·82 (0·69–0·96)	0·0166
Length of stay >12 h	115 (38%)	75 (25%)	0·64 (0·50–0·82)	0·0003	0·67 (0·51–0·86)	0·0018

Data are median (IQR) or n (%), unless indicated otherwise. *Model coefficient is either the ratio, for prednisolone relative to placebo, of geometric means (logged continuous variable) from a linear regression model or the relative risk (dichotomous variable) from a log-binomial regression. †Model adjustments include age, personal and family history of atopy, baseline pulmonary score, and presence of virus.

Table 2: **Unadjusted and adjusted model outputs for length of stay until ready for discharge (primary outcome) and sensitivity analysis (post-hoc superiority analysis)**
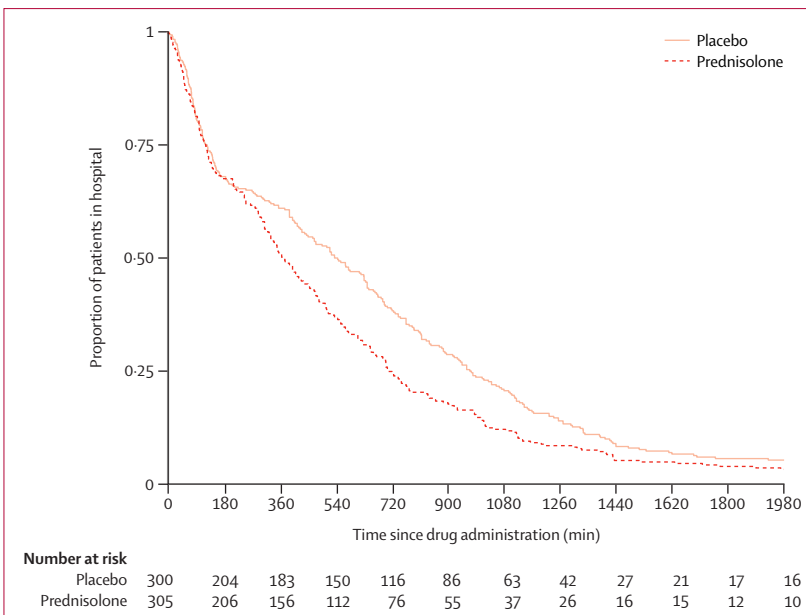
Figure 2: **Kaplan-Meier plot showing the proportion of children remaining in hospital over time within each treatment group**

ready for discharge increased (figure 2), with a separation in the curves for proportion of patients in hospital beginning at about 200 min.

The first subgroup analysis involved stratification by baseline pulmonary score with patients grouped on the basis of severity (table 3). Within the mild subgroup, prednisolone was associated with reduced risk of length of stay exceeding 12 h (adjusted RR 0·63, 95% CI 0·42–0·96; p=0·0329). The result was similar within the severe subgroup, where prednisolone was also associated with reduced risk of length of stay exceeding 7 h (0·76, 0·58–0·99; p=0·0428). The magnitude of the

effect sizes for continuous length of stay hours increased with increasing baseline wheeze severity (table 3).

A second post-hoc subgroup analysis involved stratification by whether or not inhaled salbutamol had been administered before the emergency department attendance (table 3). Within the group of patients that had received inhaled salbutamol before attending the emergency department, prednisolone was associated with an overall reduced length of stay and reduced risk of length of stay exceeding 7 h or 12 h, independent of pulmonary score at presentation, but not in patients who had not received prior salbutamol. A third subgroup analysis involved stratification by presence of viral antigen (viral antigen data available for 531 [88%] patients). Treatment efficacy was broadly similar within the viral antigen-positive and viral antigen-negative groups (table 3) and with no significant findings on the primary outcome related to type or combination of viruses detected (table 4). Prednisolone was associated with a reduced risk of length of stay exceeding 12 h in both groups (with or without presence of viral antigen; table 3). The fourth subgroup analysis involved stratification based on prior diagnosis of asthma; prednisolone was associated with a significantly reduced risk of length of stay exceeding 7 h or 12 h in the subgroup of patients with previously diagnosed asthma, but not in the subgroup of patients with no previous diagnosis (table 3).

Follow-up data up to 3 months after discharge from hospital were available for 576 of 605 patients (296 [97%] of 305 patients in the prednisolone group vs 280 [93%] of 300 patients in the placebo group). Of the 26 patients who re-attended the paediatric emergency department (15 patients in the prednisolone group vs 13 in the placebo group; p=0·85; appendix), 15 patients were discharged (nine vs six), and steroids were prescribed at re-presentation for three patients in the prednisolone group and two patients in placebo group. Similar numbers of patients who had been admitted required observation within ESSU (three vs three), were admitted to the inpatient ward (one vs three), and admitted to paediatric intensive care unit (one vs none).

No difference was seen between the groups in the follow-up secondary outcome data for total number of bronchodilator actuations in the paediatric emergency department (18·9 patients for placebo vs 18·2 patients for prednisolone; p=0·23), family doctor medical review, episodes of recurrent wheeze, or subsequent asthma diagnosis (appendix).

No serious adverse events were reported during the study or follow-up period. One child in the placebo group developed a non-specific maculopapular rash 5 h after receiving study drug, but this resolved spontaneously; this patient was withdrawn from the study at the guardian's request. Two children (one from each group) were reported to be hyperactive during follow-up assessments. 30 (5%) patients had protocol deviations and received corticosteroid during their hospital stay

	Placebo (n=300)	Prednisolone (n=305)	Unadjusted model coefficient (95% CI)*	p value	Adjusted model coefficient (95% CI)†	p value
Baseline pulmonary score <5 (mild)						
Total, min	292 (80–759)	270 (87–561)	0·89 (0·67–1·18)	0·41	0·89 (0·66–1·22)	0·48
>4 h	86 (52%)	96 (53%)	1·02 (0·83–1·24)	0·86	1·07 (0·87–1·32)	0·51
>7 h	71 (43%)	65 (36%)	0·84 (0·64–1·09)	0·18	0·83 (0·63–1·09)	0·17
>12 h	46 (28%)	31 (17%)	0·61 (0·41–0·92)	0·0182	0·63 (0·42–0·96)	0·0329
Baseline pulmonary score=5 (moderate)						
Total, min	717 (348–1108)	550 (292–870)	0·78 (0·56–1·08)	0·14	0·79 (0·56–1·13)	0·20
>4 h	65 (78%)	59 (79%)	1·00 (0·85–1·18)	0·96	1·01 (0·98–1·05)	0·51
>7 h	58 (70%)	45 (60%)	0·86 (0·68–1·08)	0·20	0·88 (0·70–1·11)	0·28
>12 h	40 (48%)	26 (35%)	0·72 (0·49–1·05)	0·09	0·76 (0·51–1·14)	0·18
Baseline pulmonary score >5 (severe)						
Total, min	890 (625–1262)	620 (305–1015)	0·66 (0·45–0·95)	0·0279	0·62 (0·41–0·95)	0·0321
>4 h	45 (88%)	40 (83%)	0·94 (0·80–1·11)	0·49	0·88 (0·75–1·04)	0·14
>7 h	41 (80%)	29 (60%)	0·75 (0·58–0·98)	0·0354	0·76 (0·58–0·99)	0·0428
>12 h	29 (57%)	18 (38%)	0·66 (0·43–1·02)	0·06	0·65 (0·42–1·00)	0·05
No salbutamol received before admission to emergency department						
Total, min	400 (110–765)	438 (100–725)	1·00 (0·70–1·43)	1·00	1·09 (0·74–1·61)	0·67
>4 h	50 (59%)	57 (66%)	1·11 (0·88–1·41)	0·37	1·17 (0·93–1·48)	0·19
>7 h	41 (48%)	46 (53%)	1·10 (0·81–1·47)	0·54	1·09 (0·80–1·47)	0·59
>12 h	24 (28%)	23 (26%)	0·94 (0·57–1·52)	0·79	0·99 (0·60–1·64)	0·98
Salbutamol received before admission to emergency department						
Total, min	615 (142–1000)	350 (125–700)	0·71 (0·56–0·92)	0·0088	0·71 (0·54–0·93)	0·0140
>4 h	146 (68%)	138 (63%)	0·93 (0·81–1·07)	0·31	0·94 (0·81–1·09)	0·42
>7 h	129 (60%)	93 (43%)	0·71 (0·59–0·86)	0·0004	0·70 (0·57–0·86)	0·0007
>12 h	91 (42%)	52 (24%)	0·56 (0·42–0·75)	<0·0001	0·56 (0·42–0·76)	0·0002
No virus detected (n=186)‡						
Total, min	545 (128–895)	325 (130–640)	0·72 (0·49–1·03)	0·08	0·72 (0·49–1·04)	0·08
>4 h	57 (64%)	60 (62%)	0·97 (0·77–1·20)	0·76	0·98 (0·79–1·22)	0·86
>7 h	48 (54%)	39 (40%)	0·75 (0·55–1·02)	0·06	0·74 (0·55–1·01)	0·06
>12 h	33 (37%)	19 (20%)	0·53 (0·33–0·86)	0·0100	0·53 (0·33–0·87)	0·0113
Virus detected (n=345)‡						
Total, min	559 (109–1032)	405 (125–750)	0·86 (0·65–1·13)	0·27	0·85 (0·65–1·13)	0·27
>4 h	116 (66%)	112 (66%)	1·01 (0·86–1·17)	0·94	1·02 (0·88–1·19)	0·76
>7 h	103 (59%)	83 (49%)	0·84 (0·69–1·02)	0·08	0·85 (0·70–1·03)	0·10
>12 h	69 (39%)	48 (28%)	0·72 (0·54–0·98)	0·0364	0·73 (0·54–0·99)	0·0395
No previously diagnosed asthma						
Total, min	570 (105–960)	430 (138–832)	0·92 (0·64–1·33)	0·67	1·00 (0·69–1·46)	1·00
>4 h	57 (64%)	66 (69%)	1·07 (0·87–1·32)	0·50	1·15 (0·94–1·41)	0·18
>7 h	51 (57%)	49 (51%)	0·89 (0·68–1·16)	0·39	0·96 (0·74–1·24)	0·74
>12 h	34 (38%)	28 (29%)	0·76 (0·51–1·15)	0·20	0·80 (0·53–1·21)	0·29
Previously diagnosed asthma						
Total, min	535 (128–972)	349 (115–699)	0·73 (0·57–0·94)	0·0143	0·71 (0·54–0·93)	0·0144
>4 h	139 (66%)	129 (62%)	0·94 (0·81–1·08)	0·37	0·92 (0·79–1·08)	0·31
>7 h	119 (56%)	90 (43%)	0·76 (0·63–0·93)	0·0069	0·73 (0·59–0·91)	0·0044
>12 h	81 (38%)	47 (23%)	0·59 (0·43–0·79)	0·0006	0·58 (0·42–0·80)	0·0008

Data are n (%) or median (IQR), unless indicated otherwise. *Model coefficient is either the ratio (95% CI), for prednisolone relative to placebo, of geometric means (logged continuous variable) from a linear regression model or the relative risk (dichotomous variable) from a log-binomial regression and 95% CI. †Model adjustments include age, personal and family history of atopy, baseline pulmonary score, and presence of virus (where appropriate). ‡Viral testing data only collected for 531 (88%) participants.

Table 3: Unadjusted and adjusted model output for length of stay until ready for discharge (primary outcome) and sensitivity analysis, by subgroup (post-hoc superiority analysis)

	Placebo (n=265)		Prednisolone (n=266)		Effect size (95% CI)*	p value†
	Patients	Length of stay, min	Patients	Length of stay, min		
Positive for virus	176/265 (66%)	..	169/266 (64%)	..	0·88 (0·62–1·26)	0·55
Rhinovirus only	133	615 (110–1065)	125	470 (155–775)	0·89 (0·65–1·21)	0·45
Respiratory syncytial virus only	7	439 (372–1000)	13	563 (335–1890)	1·05 (0·36–3·09)	0·93
Rhinovirus with another virus identified	168	559 (104–1019)	156	400 (116–736)	0·83 (0·63–1·11)	0·21
Respiratory syncytial virus with another virus identified	42	434 (94–828)	44	332 (92–706)	0·80 (0·44–1·47)	0·47
Other viruses identified in isolation	14	228 (76–828)	16	122 (77–662)	0·58 (0·17–1·98)	0·37

Data are n/N (%), n, or median (IQR), unless indicated otherwises. *Relative risk or ratio geometric means for logged length of stay for prednisolone relative to placebo. †p value calculated from a χ^2 test for categorical variables or Student's t test for continuous variables (logged).

Table 4: Descriptive statistics (including length of stay until ready for discharge) for virus detection, by virus type and treatment group (post-hoc superiority analysis)

(23 patients in the placebo group *vs* seven patients in the prednisolone group). A further 34 (6%) patients did not complete the 3-day course of study drug after discharge (19 *vs* 15) due to parental decision.

Discussion

This trial was planned and undertaken to demonstrate non-inferiority of placebo relative to a 3-day course of oral prednisolone in patients of preschool age presenting to a paediatric emergency department with a presumed virus-associated wheezing episode. With the primary hypothesis being disproved, results of a post-hoc superiority analysis (undertaken before unblinding of the data and bio-statistical staff) showed a significant reduction in length of stay until ready for discharge in children who received oral prednisolone, with the greatest effect seen in subgroup analysis in patients with features of severe wheeze or prior history of asthma. We found no apparent effect of oral steroids on reducing the incidence of short stays (<4 h) in post-hoc sensitivity analysis, which is probably because the patients who had short visits had the mildest symptoms. The likelihood of the hospital stays exceeding 7 h or 12 h was significantly reduced in the prednisolone group compared with the placebo group in the post-hoc sensitivity analysis, and the median length of stay for the prednisolone group was nearly 3 h (170 min) shorter in the prednisolone group than the placebo group. The absolute reduction in the percentage of patients with a length of stay exceeding 12 h (13%) represents a number needed to treat of about eight patients to prevent the length of stay of one patient exceeding 12 h.

These findings might appear to contradict those of a previous study of a 678 patient cohort,[14] in which no statistically significant reduction in hospital stay was found for those receiving prednisolone. However, comparison of confidence intervals between the datasets reveals substantial overlap, and the overall findings should be considered broadly consistent. The present study was powered to detect a ratio of 0·85, but we

observed and report a ratio of 0·79, which suggests a larger effect than anticipated but with an increased variability, as shown by the upper bound of the 95% CI approaching 1 (95% CI 0·64–0·97), whereas Panickar and colleagues[14] report an unadjusted ratio of 0·90 (95% CI 0·77–1·05).

The superiority of prednisolone in this study could be explained by our study design to address the limitations identified in the previous study,[14] which had led to concerns with the generalisability of their conclusions.[22] To address some of these limitations, our study design included an entry age limit of 2 years rather than 10 months as in the study by Panickar and colleagues[14] to reduce the likelihood of including patients with bronchiolitis, which occurs in children younger than 2 years[23] and for whom corticosteroid use is known to be ineffective.[24] We also included patients with markers of moderate-to-severe wheezing episodes to allow findings to be applied across a broad range of wheeze severity presentations. The recording of wheeze severity using the pulmonary score before any bronchodilator therapy was given in the emergency department provided an objective assessment of the severity at the point of entry to the emergency department, both in patients who had received therapies before admission and those who had not. Further studies will be necessary to determine which subgroups of children with heterogeneous wheeze aged 1–2 years would potentially benefit from steroids.

In subgroup analyses, the significant reduction in length of stay after prednisolone treatment in patients who had received treatment with inhaled bronchodilators before admission to the paediatric emergency department identifies a cohort that had already shown suboptimal bronchodilator response and would benefit from early administration of oral corticosteroid therapy to reduce the length of stay in hospital; the reduction with prednisolone treatment in the proportion of patients with a length of stay exceeding 12 h was larger in the group of patients who had received bronchodilators

before coming to the emergency department (18%) and in patients with high baseline pulmonary score (19%) than the overall reduction in the number of patients with length of stay exceeding 12 h (13%; table 2; table 3). This reduction was also seen in patients with prior history of asthma (15%). These data suggest a number needed to treat (within these categories) of about six patients. Although the findings are compelling, we note that the sample size was smaller for these subgroup analyses than the primary analysis. Despite there being equal distribution of patients between placebo and treatment groups for these subgroup analyses, patients were not randomly assigned to treatment group primarily on the basis of either wheeze severity at presentation or salbutamol use before admission to the emergency department.

Family history or personal history of atopy have previously been identified as major risk factors[25] for further episodes of wheeze after preschool age. When these factors were included in the statistical model, the main effect estimate for prednisolone was not significantly altered (table 2, appendix). These factors do not, at preschool age, appear to significantly modify steroid responsiveness in the setting of a virus-associated wheezing episode. Findings in previous studies[3] have suggested steroid responsiveness might be organism-dependent. In the two-thirds of the study patients tested for viral antigen, a triggering virus was identified and yet we found no significant difference in length of stay by virus type in subgroup analysis (table 4).

The strengths of our study include the large sample size, broadly applicable inclusion criteria, and a comprehensive set of outcomes with a high rate of successful follow-up. However, the limitations of this study relate to the study being done in a single centre and to recruitment difficulties due to dependence on clinical staff in a busy paediatric emergency department remembering to recruit. Rotational staff also needed repeated training of the study protocols to achieve consistent recruitment. These factors resulted in a high non-participation rate. 5% of patients had a protocol deviation whereby they received prednisolone after receiving the study drug. All these patients were admitted and the inpatient clinicians chose to alter treatment as per protocol. The larger number of patients who had received placebo might have reduced the ability to measure the effect of prednisolone on outcomes. The pulmonary score was used to assess wheeze severity as it had previously been instituted into departmental protocols. This score has been validated in children aged 5 years and older,[18] but is not fully validated in children younger than 5 years; it follows that our categorisation of mild, moderate, and severe is not validated within this tool. The three variables were broadly similar to other paediatric wheeze severity scoring systems, and to minimise confusion for clinical staff, we chose to continue with using the score already established within the department. The follow-up data were not complete, but more than 95% of patients had a minimum of one follow-up contact.

In conclusion, oral prednisolone had a clear benefit compared with placebo in reducing the length of stay in children presenting to a paediatric emergency department with virus-associated wheeze, with the greatest efficacy seen in patients with either severe features of wheeze at presentation, receiving salbutamol before presentation, or prior history of asthma. Past or family history of atopy or the presence of a virus on sampling were not predictors of steroid responsiveness, and no other significant predictors were found.

References
1 Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995; **332:** 133–38.
2 Bisgaard H, Szefler S. Prevalence of asthma-like symptoms in young children. *Pediatr Pulmonol* 2007; **42:** 723–28.
3 Jartti T, Lehtinen P, Vanto T, et al. Efficacy of prednisolone in children hospitalized for recurrent wheezing. *Pediatr Allergy Immunol* 2007; **18:** 326–34.
4 Hogg C, Bush A. Childhood asthma—all that wheezes is not inflammation. *Clin Exp Allergy* 1997; **27:** 991–94.
5 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:** 317–20.
6 Stevenson EC, Turner G, Heaney LG, et al. Bronchoalveolar lavage findings suggest two different forms of childhood asthma. *Clin Exp Allergy* 1997; **27:** 1027–35.
7 Saglani S, Malmström K, Pelkonen AS, et al. Airway remodelling and inflammation in symptomatic infants with reversible airflow obstruction. *Am J Respir Crit Care Med* 2005; **171:** 722–27.
8 Maclennan C, Hutchinson P, Holdsworth S, Bardin PG, Freezer NJ. Airway inflammation in asymptomatic children with episodic wheeze. *Pediatr Pulmonol* 2006; **41:** 577–83.
9 Le Bourgeois M, Goncalves M, Le Clainche L, et al. Bronchoalveolar cells in in children <3 years old with severe recurrent wheezing. *Chest* 2002; **122:** 791–97.
10 Rowe BH, Spooner C, Ducharme F, Bretzlaff J, Bota G. Early emergency department treatment of acute asthma with systemic corticosteroids. *Cochrane Database Syst Rev* 2001; **1:** CD002178.
11 Smith M, Iqbal S, Elliott TM, Everard M, Rowe BH. Corticosteroids for hospitalised children with acute asthma. *Cochrane Database Syst Rev* 2003; **1:** CD002886.
12 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:** 725–30.
13 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:** 482–88.

14   Panickar J, Lakhanpaul M, Lambert PC, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. *N Engl J Med* 2009; **360:** 329–38.

15   Ducharme FM, Zemek RL, Schuh S. Oral corticosteroids in children with wheezing. *N Engl J Med* 2009; **360:** 1674.

16   British Thoracic Society, Scottish Intercollegiate Guidelines Network. A national clinical guideline. https://www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2014/ (accessed Dec 3, 2017).

17   National Asthma Council Australia. The Australian Asthma Handbook, version 1.1. Melbourne, VIC: National Asthma Council Australia, 2015.

18   Smith SR, Baty JD, Hodge D 3rd. Validation of the pulmonary score: an asthma severity score for children. *Acad Emerg Med* 2002; **9:** 99–104.

19   Chidlow GR, Harnett GB, Shellam GR, Smith DW. An economical tandem multiplex real-time pcr technique for the detection of a comprehensive range of respiratory pathogens. *Viruses* 2009; **1:** 42–56.

20   Maumill L, Zic M, Esson AA, et al. The National Emergency Access Target (NEAT): can quality go with timeliness? *Med J Aust* 2013; **198:** 153–57.

21   Thabane L, Mbuagbaw L, Zhang S, et al. A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. *BMC Med Res Methodol* 2013; **13:** 92.

22   Ducharme FM, Zemek R, Gravel J, et al. Determinants Of Oral corticosteroid Responsiveness in Wheezing Asthmatic Youth (DOORWAY): protocol for a prospective multicentre cohort study of children with acute moderate-to-severe asthma exacerbations. *BMJ Open* 2014; **4:** e004699.

23   National Institute for Health and Clinical Excellence. Bronchiolitis in children: diagnosis and management NICE guideline [NG9]. June, 2015. www.nice.org.uk/guidance/ng9 (accessed Dec 3, 2017).

24   Fernandes RM, Bialy LM, Vandermeer B, et al. Glucocorticoids for acute viral bronchiolitis in infants and young children. *Cochrane Database Syst Rev* 2013; **6:** CD004878.

25   Castro-Rodríguez 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:** 1403–06.