Efficacy of oral corticosteroids for acute preschool wheeze: a systematic review and individual participant data meta-analysis of randomised clinical trials

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Summary

Background Oral corticosteroids are commonly used for acute preschool wheeze, although there is conflicting evidence of their benefit. We assessed the clinical efficacy of oral corticosteroids by means of a systematic review and individual participant data (IPD) meta-analysis.

Methods In this systematic review with IPD meta-analysis, we systematically searched eight databases (PubMed, Ovid Embase, CINAHLplus, CENTRAL, ClinicalTrials.gov, EudraCT, EU Clinical Trials Register, WHO Clinical Trials Registry) for randomised clinical trials published from Jan 1, 1994, to June 30, 2020, comparing oral corticosteroids with placebo in children aged 12 to 71 months with acute preschool wheeze in any setting based on the Population, Intervention, Comparison, Outcomes framework. We contacted principal investigators of eligible studies to obtain deidentified individual patient data. The primary outcome was change in wheezing severity score (WSS). A key secondary outcome length of hospital stay. We also calculated a pooled estimate of six commonly reported adverse events in the follow-up period of IPD datasets. One-stage and two-stage meta-analyses employing a random-effects model were used. This study is registered with PROSPERO, CRD42020193958.

Findings We identified 16 102 studies published between Jan 1, 1994, and June 30, 2020, from which there were 12 eligible trials after deduplication and screening. We obtained individual data from seven trials comprising 2172 children, with 1728 children in the eligible IPD age range; 853 (49·4%) received oral corticosteroids (544 [63·8%] male and 309 [36·2%] female) and 875 (50·6%) received placebo (583 [66·6%] male and 292 [33·4%] female). Compared with placebo, a greater change in WSS at 4 h was seen in the oral corticosteroids group (mean difference –0·31 [95% CI –0·38 to –0·24]; p=0·011) but not 12 h (–0·02 [–0·17 to 0·14]; p=0·68), with low heterogeneity between studies (I^2=0%; τ^2<0·001). Length of hospital stay was significantly reduced in the oral corticosteroids group (–3·18 h [–4·43 to –1·93]; p=0·0021; I^2=0%; τ^2<0·001). Subgroup analyses showed that this reduction was greatest in those with a history of wheezing or asthma (–4·54 h [–5·57 to –3·52]; $p_{interaction}$=0·0007). Adverse events were infrequently reported (four of seven datasets), but oral corticosteroids were associated with an increased risk of vomiting (odds ratio 2·27 [95% CI 0·87 to 5·88]; τ^2<0·001). Most datasets (six of seven) had a low risk of bias.

Interpretation Oral corticosteroids reduce WSS at 4 h and length of hospital stay in children with acute preschool wheeze. In those with a history of previous wheeze or asthma, oral corticosteroids provide a potentially clinically relevant effect on length of hospital stay.

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Introduction

Oral corticosteroids are beneficial in treating acute wheeze associated with asthma (typically observed in children aged ≥6 years),[1] but have no effect in treating acute wheeze associated with bronchiolitis (typically observed in children aged <12 months).[2] In preschool children aged 12–71 months, acute episodes of wheeze are common; one in three children aged 3 years or younger and one in six aged 6 years of age experience acute wheeze, which is often associated with viral infection.[3,4] Short courses of oral corticosteroids are widely used as a treatment for acute wheeze in children aged 12–71 months (acute preschool wheeze); however, it is unclear whether and to what extent oral corticosteroids are beneficial for acute preschool wheeze.[5]

Trials of oral corticosteroids in participants with acute preschool wheeze have yielded discordant results, which were reported in an evidence synthesis of ten trials published from 1986 to 2013.[6] A large UK trial showed no significant benefit of oral corticosteroids administered in the emergency department in either reducing length of hospital stay or improving the Pediatric Respiratory Assessment Measure (PRAM) score.[7] Concerns were

Research in context

Evidence before this study

Oral corticosteroids are commonly prescribed for acute preschool wheeze (in children aged 12–71 months) but are controversial as the evidence of benefit is variable and there are clinical concerns regarding side-effects. We searched PubMed and Embase between Jan 1, 1994, and Dec 31, 2020, for randomised controlled trials and systematic reviews of oral corticosteroids in acute preschool wheeze (using the search terms "wheeze OR asthma" AND "oral corticosteroids OR prednisolone") in children aged up to 12 years without language restriction. We identified one systematic review, which could not provide evidence due to significant trial heterogeneity and small sample sizes. 11 randomised controlled trials of oral corticosteroids versus placebo have been published before and after this systematic review with conflicting results, showing no effect on short-term or long-term clinical outcomes in six trials and some short-term positive clinical benefit in five trials. However, clinical trials have been highly heterogeneous in age range, setting, and outcomes, making evidence synthesis infeasible.

Added value of this study

This individual participant data (IPD) meta-analysis of seven clinical trials provides more reliable evidence with adequate statistical power to demonstrate statistically significant effects of oral corticosteroids on short-term outcomes (eg, improvement in wheezing severity and reduction in length of hospital stay) in the overall population. These short-term outcomes were greater in those with moderate-to-severe wheeze and when oral corticosteroids were provided in the emergency department. The data show that children with a history of previous wheeze or asthma received most benefit from oral corticosteroids in terms of improvement in length of hospital stay, approximating a previously identified minimal clinically important difference. Evidence for long-term benefits, especially for those without these risk factors, was not found. There was a higher risk of vomiting with oral corticosteroids, but no other adverse effects were identified.

Implications of all the available evidence

This IPD meta-analysis shows that the use of oral corticosteroids improved short-term outcomes in acute preschool wheeze, most prominently in those with previous wheeze or asthma and those presenting with moderate-to-severe acute wheeze. The use of oral corticosteroids in low-risk preschool children and those with mild acute wheeze could be deferred. Global guidelines could align to recommend the early use of oral corticosteroids in preschool children with a history of previous wheeze or asthma, particularly in those showing moderate-to-severe wheeze. More evidence is required on the adverse effects of oral corticosteroids in acute preschool wheeze, particularly when repeat doses are used.

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raised about the applicability of this study's findings in clinical practice due to the low numbers of children with moderate-to-severe wheeze and the potential inclusion of those who had bronchiolitis (considered unresponsive to steroids).[8,9] Since this first meta-analysis, several trials have been conducted. An Australian trial, the Prednisolone Response Evaluation in Viral Induced Episodic Wheeze study (PREVIEW), attempted to address these issues by including children aged 24–72 months and measuring length of hospital stay by baseline severity. PREVIEW demonstrated a significant reduction in length of hospital stay in those receiving oral corticosteroids, but only from post-hoc superiority analysis.[10] A 2020 New Zealand trial, Wheeze and Steroids in Preschoolers (WASP), showed no differential treatment effect of oral corticosteroids for length of hospital stay or PRAM score at 24 h in children who were hospitalised with acute preschool wheeze, but did find reduced 4 h PRAM scores and quicker emergency department discharge times for those sent home.[11] Despite large sample sizes, these studies did not show evidence of treatment effect by baseline severity at hospital presentation, with continuing conflicting interpretations.[8,12,13]

This uncertain evidence is reflected in a clinical tension between prescribing a treatment that might be effective and withholding because of concern about adverse effects of oral corticosteroids, particularly in those with repeat episodes of wheeze. The proportion of physicians prescribing oral corticosteroids for acute preschool wheeze in the emergency department varies from 12% to 81% depending on the scenario.[14] Without consistent supporting evidence, national clinical guidelines interpret evidence using a cautious risk–benefit approach, typically recommending oral corticosteroid use only for acute preschool wheeze requiring hospital admission (appendix p 4). However, determining at presentation which children will require hospital admission is not always straightforward, limiting the early use of oral corticosteroids in emergency departments. By contrast, the international Global Initiative for Asthma recommends that oral corticosteroids are used for all children with acute preschool wheeze attending emergency departments,[15] without consideration of baseline severity or risk factors, which might intensify clinical unease about potential overuse in milder wheeze.

We aimed to assess oral corticosteroid efficacy for acute preschool wheeze in children aged 12–71 months by conducting a systematic review and individual participant data (IPD) meta-analysis to mitigate heterogeneous baseline characteristics among the children from previous trials and systematic reviews, thus enhancing the reliability of the evidence.

See Online for appendix

Methods

Search strategy and selection process

In this systematic review with IPD meta-analysis, we searched literature published between Jan 1, 1994, and June 30, 2020, in PubMed, Ovid Embase, CINAHLplus, CENTRAL, ClinicalTrials.gov, EudraCT, EU Clinical Trials Register, and the WHO International Clinical Trials Registry Platform, along with grey literature and reference screening, for randomised clinical trials focusing on phenotypes of preschool wheeze.[3] Search strategies were developed based on the Population, Intervention, Comparison, Outcomes framework without language restriction (appendix pp 9–11). The search strategy was reviewed by a librarian at the University of Edinburgh. Eligible randomised controlled trials included children aged 12–71 months presenting with acute wheeze and compared oral corticosteroids with placebo (appendix p 12). After deduplication, two independent reviewers (BL and JT-P) screened the title and abstracts; full-text screening based on the eligibility criteria (appendix p 12) was then done using Covidence software.

This systematic review with IPD meta-analysis, registered with PROSPERO (CRD42020193958), adheres to a predetermined analysis plan (appendix pp 1–3). This study follows the Preferred Reporting Items for a Review and Meta-analysis of Individual Participant Data statement (appendix pp 5–8). The study was approved by the Usher Institute Medical School Research Ethics Committee, University of Edinburgh, UK (2112).

Data analysis

The overall process of data collection is summarised in the appendix (p 26). We contacted study investigators to request deidentified individual participant datasets. Each incoming dataset was checked for major errors, completeness, and missing data, and cleaned to ensure baseline and follow-up information was in an acceptable state for analysis. To validate accuracy, we compared the demographic characteristics and primary outcomes of each dataset to those reported in the original article. Datasets were harmonised using unified coding. For example, we standardised the units of values and coding (no=0 and yes=1). We extracted data on children or family information, such as age in months, sex, history of asthma, wheeze, eczema, hay fever, pets in the family home, and food allergy; previous presentation to general practice or emergency department or previous hospital admission due to acute wheeze; virus identification information (human rhinovirus or respiratory syncytial virus); baseline wheezing severity score (WSS) if available; and parental history of eczema or atopic eczema, asthma, hay fever, food allergy, and smoking. In addition, we collected data about the trial to access the information, such as children who were randomly assigned, whether they were included in or excluded from the original analyses, and the reasons for exclusions. By checking this information, we identified eligible children for our analysis. All variables were managed using a data dictionary shared with study investigators and a spreadsheet was used for the data extraction.

Risk of bias was assessed by two independent reviewers (BL and JT-P) using the Cochrane Risk of Bias tool for the original articles at the study level and a tailored Cochrane Risk of Bias 2 tool for the IPD.[16] Any disagreement was resolved through consensus or third-party adjudication (SC and SL).

Each contributing study was approved by the relevant medical ethics committee in accordance with the legislation of each country. Where necessary, the contributing investigators obtained further ethical approvals to enable data sharing.

During early data extraction of contributing studies for the systematic review, we identified significant heterogeneity of reported primary and secondary outcomes. To prioritise outcomes, we conducted an international survey of 253 board-certified paediatricians and convened a group discussion between the seven study investigators and nine parents of children who had experience with oral corticosteroid courses due to acute preschool wheeze. As a result, the primary outcome was determined as the change in WSS at 4 h and 12 h after oral corticosteroid administration. Key secondary outcomes included length of hospital stay (in h), revisits to general practice or emergency department, rehospitalisation, time back to normal (defined by parents, in days), doses of short-acting β_2 agonist during 7 and 14 days, need for additional steroids, and adverse events. Other outcomes reported in the original articles could not be addressed in our analyses because too few data were available. Short-term outcomes were those reported up to and including hospital discharge, with long-term outcomes those reported after hospital discharge.

Change in WSS was calculated by subtracting the baseline WSS from the final WSS at 4 h or 12 h. Various scoring tools, including PRAM (score range 0–12),[17] Pulmonary Score (score range 0–9),[18] and Respiratory Symptoms Score (RSS; score range 0–12),[19] were used in contributing studies. Different scales were standardised for comparison by transforming the data into a single continuous scoring scale that adheres to the range defined by PRAM. This transformation and methodology are detailed in the appendix (p 13).[20]

We incorporated all randomly assigned participants not included in the original article as long as they met our eligibility criteria and we analysed treatment effects of oral corticosteroids using the intention-to-treat approach. We presented effects as odds ratios (ORs) for binary outcomes and mean differences for continuous outcomes, with 95% CIs. For the primary outcome and a key secondary outcome (length of hospital stay), we conducted an aggregated meta-analysis using the reported aggregate data to compare the results with those of IPD meta-analysis.

Our IPD meta-analysis followed a two-stage approach. In the first stage, we applied standardised multivariable regression models to each dataset, adjusting for age (months), a history of allergy (atopic eczema or eczema, hay fever, or any food allergy) and parental allergies (eczema, hay fever, or food allergy) or asthma. In the second stage, we synthesised all estimates using a random-effects model based on the inverse-variance approach. We assessed heterogeneity by employing the restricted maximum likelihood with the Hartung-Knapp-Sidik-Jonkman adjustment. To address systemic missing variables, we grouped related variables together to increase the power of analysis. In the one-stage approach, a generalised linear mixed model fit by maximum likelihood was used to analyse all trials simultaneously, accounting for the clustering of patients within trials to validate results from two-stage methods and handle analyses with rare events. The fixed baseline risk and random treatment effects were used in the model.

The amount of heterogeneity between the treatment effects in different randomised controlled trials was assessed using τ^2 with Cochrane's Q test and the assumption of homogeneity was rejected when the p value was less than 0·10.[21] I^2 was presented to show the proportion of total variation between estimates due to between-study heterogeneity. Sensitivity analyses were done for common-effects models, regression models, and study settings. For trials in which IPD could not be obtained, our initial plan was to approach the study investigators, requesting that they perform the same statistical models and provide the estimates. However, this approach proved infeasible due to either a lack of response or the unavailability of the dataset. Therefore, relevant aggregate data from their reports were incorporated in the second stage of a two-stage meta-analysis approach as a sensitivity analysis. Prespecified subgroup analyses and treatment-covariate interaction assessments were conducted to identify potential variables contributing to oral corticosteroid effects and reduce the risk of ecological bias, although they inevitably lack power and can show spurious effects due to multiple testing. Therefore, we have taken due care in their interpretation. We set the significance threshold at 5% (two-sided) for the outcomes. The quality of evidence for the key outcomes was graded using GRADEpro software.[22] All analyses were done using R (4.2.2). We used R package meta and lme4 for the IPD meta-analysis.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From the initial 16 102 studies identified in our search between Jan 1, 1994, and June 30, 2020, we identified 12 eligible trials after deduplication and screening (figure 1).[7,10,11,19,23–30] One study, the Oral Corticosteroids for Treating Episodes of Significant Lower Respiratory Tract Symptoms (OCELOT), was prematurely halted, but we decided to include IPD of this study for children who completed the intervention per protocol.[30] The aggregate data from 11 eligible trials were available for the systematic review with aggregated meta-analysis (OCELOT did not report results; appendix p 14), with wide variation of the inclusion age range (appendix p 27). Our primary outcome, change in WSS, was reported in three trials that used different scoring systems and incompatible statistical metrics, preventing a summary evaluation.[7,11,24] Our key

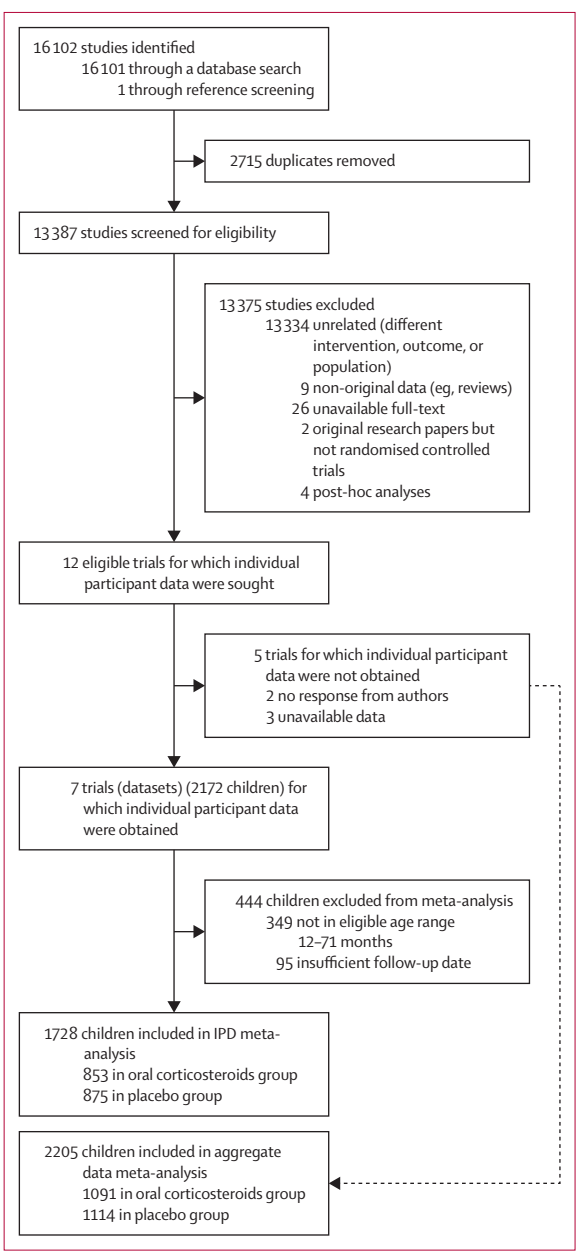

Figure 1: **Study selection**

	Csonka[27] (n=158)		Oommen[28] (n=121)*		VINKU1[19] (n=198)†		Panickar[7] (n=541)		VINKU2[29] (n=44)†		PREVIEW[10] (n=605)		OCELOT[30] (n=61)‡	
	Placebo (n=78)	Oral corticosteroids (n=80)	Placebo (n=69)	Oral corticosteroids (n=52)	Placebo (n=101)	Oral corticosteroids (n=97)	Placebo (n=264)	Oral corticosteroids (n=277)	Placebo (n=23)	Oral corticosteroids (n=21)	Placebo (n=300)	Oral corticosteroids (n=305)	Placebo (n=40)	Oral corticosteroids (n=21)
Family information														
Parental eczema or atopic eczema	35/75 (46·7%)	35/70 (50·0%)	39/42 (92·9%)	31/36 (86·1%)	48/95 (50·5%)	53/90 (58·9%)	NA	NA	8/18 (44·4%)	7/14 (50·0%)	90/273 (33·0%)	93/290 (32·1%)	24/39 (61·5%)	12/19 (63·2%)
Parental asthma	12/75 (16·0%)	9/70 (12·9%)	51/68 (75·0%)	42/52 (80·8%)	26/99 (26·3%)	20/95 (21·1%)	111/259 (42·9%)	118/264 (44·7%)	6/23 (26·1%)	5/21 (23·8%)	180/287 (62·7%)	185/298 (62·1%)	15/40 (37·5%)	16/21 (76·2%)
Parental hay fever	24/75 (32·0%)	24/70 (34·3%)	15/42 (35·7%)	18/36 (50·0%)	34/91 (37·4%)	37/85 (43·5%)	NA	NA	14/23 (60·9%)	15/21 (71·4%)	107/270 (39·6%)	94/286 (32·9%)	24/39 (61·5%)	12/19 (63·2%)
Parental food allergy	10/75 (13·3%)	10/70 (14·3%)	3/42 (7·1%)	4/36 (11·1%)	NA	NA	NA	NA	4/17 (23·5%)	3/12 (25·0%)	40/271 (14·8%)	42/284 (14·8%)	NA	NA
Pets in the family home	13/75 (17·3%)	17/70 (24·3%)	33/68 (48·5%)	22/52 (42·3%)	35/98 (35·7%)	25/94 (26·6%)	NA	NA	5/23 (21·7%)	6/21 (28·6%)	NA	NA	20/40 (50·0%)	11/21 (52·4%)
Parental smoking	36/76 (47·4%)	24/70 (34·3%)	34/69 (49·3%)	22/52 (42·3%)	40/100 (40·0%)	40/96 (41·7%)	92/259 (35·5%)	91/266 (34·2%)	9/23 (39·1%)	12/21 (57·1%)	96/300 (32·0%)	96/305 (31·5%)	11/40 (27·5%)	8/21 (38·1%)
Child information														
Mean age, months (SD)	20·5 (6·3)	20·4 (5·9)	28·8 (12·2)	27·9 (12·7)	27·4 (12·5)	27·0 (13·5)	29·1 (14·4)	28·1 (12·9)	15·9 (2·9)	18·9 (3·7)	40·9 (13·0)	40·8 (12·6)	33·9 (15·6)	34·3 (16·7)
Sex														
Male	50/78 (64·1%)	46/80 (57·5%)	47/69 (68·1%)	31/52 (59·6%)	66/101 (65·3%)	64/97 (66·0%)	167/264 (63·3%)	174/277 (62·8%)	19/23 (82·6%)	14/21 (66·7%)	209/300 (69·7%)	199/305 (65·2%)	25/40 (62·5%)	16/21 (76·2%)
Female	28/78 (35·9%)	34/80 (42·5%)	22/69 (31·9%)	21/52 (40·4%)	35/101 (34·7%)	33/97 (34·0%)	97/264 (36·7%)	103/277 (37·2%)	4/23 (17·4%)	7/21 (33·3%)	91/300 (30·3%)	106/305 (34·8%)	15/40 (37·5%)	5/21 (23·8%)
History of asthma	0/78 (0%)	0/80 (0%)	25/69 (36·2%)	16/52 (30·8%)	28/85 (32·9%)	33/84 (39·3%)	47/259 (18·1%)	55/267 (20·6%)	0/23 (0%)	0/21 (0%)	80/300 (26·7%)	65/305 (21·3%)	23/40 (57·5%)	14/21 (66·7%)
History of wheeze	47/76 (61·8%)	42/71 (59·2%)	55/69 (79·7%)	44/52 (84·6%)	101/101 (100%)	97/97 (100%)	182/259 (70·3%)	178/266 (66·9%)	0/23 (0%)	0/21 (0%)	211/300 (70·3%)	209/305 (68·5%)	40/40 (100%)	21/21 (100%)
History of eczema	37/77 (48·1%)	34/74 (45·9%)	27/69 (39·1%)	17/52 (32·7%)	50/99 (50·5%)	40/96 (41·7%)	116/257 (45·1%)	115/264 (43·6%)	9/23 (39·1%)	9/21 (42·9%)	105/300 (35·0%)	89/305 (29·2%)	23/39 (59·0%)	12/21 (57·1%)
History of hay fever	1/78 (1·3%)	1/80 (1·2%)	60/69 (93·8%)	45/52 (91·8%)	15/97 (15·5%)	13/93 (14·0%)	20/246 (8·1%)	22/258 (8·5%)	2/18 (11·1%)	1/14 (7·1%)	28/300 (9·3%)	17/305 (5·6%)	16/36 (44·4%)	4/16 (25·0%)
History of food allergy	27/76 (35·5%)	22/74 (29·7%)	54/69 (78·3%)	46/52 (88·5%)	40/96 (41·7%)	34/94 (36·2%)	22/254 (8·7%)	29/262 (11·1%)	8/23 (34·8%)	7/21 (33·3%)	52/300 (17·3%)	42/305 (13·8%)	9/38 (23·7%)	2/19 (10·5%)
Previous presentation to general practice or emergency department	38/75 (50·7%)	36/69 (52·2%)	69/69 (100%)	52/52 (100%)	12/62 (19·4%)	21/73 (28·8%)	159/257 (61·9%)	155/265 (58·5%)	0/23 (0%)	0/21 (0%)	NA	NA	39/40 (97·5%)	21/21 (100%)
Previous hospital admission	18/76 (23·7%)	17/71 (23·9%)	25/53 (47·2%)	20/44 (45·5%)	11/62 (17·7%)	16/73 (21·9%)	96/258 (37·2%)	85/268 (31·7%)	0/23 (0%)	0/21 (0%)	188/300 (62·7%)	182/305 (59·7%)	7/40 (17·5%)	3/21 (14·3%)
Virus identification: human rhinovirus only	NA	NA	NA	NA	28/101 (27·7%)	23/97 (23·7%)	NA	NA	17/23 (73·9%)	15/21 (71·4%)	134/175 (76·8%)	125/169 (74·0%)	NA	NA
Virus identification: respiratory syncytial virus	NA	NA	NA	NA	10/101 (9·9%)	8/97 (8·2%)	NA	NA	0/23 (0%)	0/21 (0%)	7/175 (4·0%)	13/169 (7·7%)	NA	NA

(Table 1 continues on next page)

secondary outcome, length of hospital stay was reported in eight trials,[7,10,11,19,23,25–27] in which incompatible statistical metrics meant that only three trials were available for aggregation (appendix p 28).[7,23,25] In these three trials, length of hospital stay was reduced by 0·27 h (95% CI –0.80 to 0.27) in individuals receiving oral corticosteroids. Of the 12 eligible trials, the contributing investigators of nine trials responded when contacted. Investigators in three trials reported that their datasets (published in 1994 and 1995) were destroyed or lost[23–25] and six agreed to share their datasets,[7,10,19,27–29] with one having two datasets (VINKU1 and VINKU2). Investigators in two trials did not respond to multiple contact attempts.[11,26] Subsequently, a total of seven datasets were included for IPD analysis. Three datasets from Finland (Csonka, VINKU1, and VINKU2),[19,27,29] two from the UK (Oommen and Panickar),[7,28] one from Australia (PREVIEW),[10] and one from the USA (OCELOT).[30] Five studies were emergency department or in-patient based and two were community based (appendix pp 15–16). For the five unavailable datasets, we initially intended to incorporate estimates from the original articles into the pooled estimates in the sensitivity analyses. However, only one study (WASP)[11] was incorporated, as the estimates from the other four studies[23–26] were incompatible due to different statistical approaches.

The seven contributing datasets contained data for 2172 individual patients (appendix pp 15–16), of which 1728 participants were within the eligible IPD age range (12–71 months) and were included in the meta-analysis. 853 (49·4%) participants received oral corticosteroids and 875 (50·6%) received placebo (table 1). All studies used prednisolone as an intervention. Quality assessment results of the included studies for the systematic review and IPD meta-analysis are summarised in the appendix (pp 14, 17). Most (six of seven) of the included databases in the IPD meta-analysis had a low risk of bias. Although one study exclusively recruited children with first acute wheeze,[29] three exclusively included children with recurrent wheeze,[19,28,30] and the remaining three had more than 68% (869 of 1277) of participants with recurrent wheeze.[7,10,27] Baseline WSS was measured in four datasets (table 1).[7,10,19,29] Three datasets included predominantly children with moderate-to-severe wheeze (VINKU1 187 [94·4%] of 198; VINKU2 35 [79·5%] of 44; Panickar 325 [60·9%] of 534),[7,19,29] and, in one dataset (PREVIEW), 348 (57·5%) of the 605 participants had mild wheeze.[10]

Compared with placebo, a greater change in WSS at 4 h was seen in the oral corticosteroids group (mean difference –0·31 [95% CI –0·38 to –0·24]; p=0·011; 528 children in two studies;[7,10] table 2). By 12 h, there was no evidence of difference in change in WSS between the two groups (mean difference –0·02 [–0·17 to 0·14]; p=0·68; 472 children in three studies).[7,10,19]

	Csonka[27] (n=158)		Oommen[28] (n=121)*		VINKU1[19] (n=198)†		Panickar[7] (n=541)		VINKU2[29] (n=44)†		PREVIEW[10] (n=605)		OCELOT[30] (n=61)‡	
	Placebo (n=78)	Oral corticosteroids (n=80)	Placebo (n=69)	Oral corticosteroids (n=52)	Placebo (n=101)	Oral corticosteroids (n=97)	Placebo (n=264)	Oral corticosteroids (n=277)	Placebo (n=23)	Oral corticosteroids (n=21)	Placebo (n=300)	Oral corticosteroids (n=305)	Placebo (n=40)	Oral corticosteroids (n=21)
(Continued from previous page)														
Baseline wheezing severity score (scale; participants)§	No	No	No	No	Yes (RSS; 101)¶	Yes (RSS; 97)¶	Yes (PRAM; 261)‖	Yes (PRAM; 273)‖	Yes (RSS; 23)¶	Yes (RSS; 21)¶	Yes (Pulmonary Score; 300)**	Yes (Pulmonary Score; 305)**	No	No
Median (IQR)	NA	NA	NA	NA	7 (5–8)	7 (5–7)	4 (3–6)	4 (3–6)	6 (4–7)	6 (4–8)	4 (3–5)	4 (3–5)	NA	NA
Mild classification	NA	NA	NA	NA	2/101 (2·0%)	9/97 (9·3%)	102/261 (39·1%)	107/273 (39·2%)	4/23 (17·4%)	5/21 (23·8%)	166/300 (55·3%)	182/305 (59·7%)	NA	NA
Moderate classification	NA	NA	NA	NA	72/101 (71·3%)	66/97 (68·0%)	137/261 (52·5%)	137/273 (50·2%)	16/23 (69·6%)	9/21 (42·9%)	83/300 (27·7%)	75/305 (24·6%)	NA	NA
Severe classification	NA	NA	NA	NA	27/101 (26·7%)	22/97 (22·7%)	22/261 (8·4%)	29/273 (10·6%)	3/23 (13·0%)	7/21 (33·3%)	51/300 (17·0%)	48/305 (15·7%)	NA	NA

Data are n or n (%), unless otherwise specified. Denominators represent the total number without missing data. NA=not available. PRAM=Paediatric Respiratory Assessment Measure. RSS=Respiratory Symptoms Score. *Patients were included in the analysis of the published paper. †All randomly assigned patients. ‡Patients received OCELOT treatment in a per-protocol fashion; the primary outcome was PRAM scores measured 36–72 h after initiation of intervention, but baseline PRAM scores were not available. §Original scales before standardisation. ¶Baseline wheezing severity score was measured using the RSS tool (scale 0–12); RSS does not have actual severity classes; by comparing the components and scales with those of PRAM, we applied the cutoffs of PRAM. ‖Baseline severity score was measured using the PRAM scoring tool (scale 0–12). **Baseline wheezing severity score was obtained using the Pulmonary Score tool (scale 0–9).

Table 1: **Study designs and patient characteristics of children aged 12–71 months**

	Oral corticosteroids group (n=853)	Placebo group (n=875)	Studies (patients), n	Combined odds ratio* or mean difference† (95% CI)	p value	I^2	τ^2
Change in WSS in 4 h	–1·94 (2·15); 282	–1·63 (2·02); 246	2 (528)	–0·31 (–0·38 to –0·24)†	0·011	0·0%	<0·001
Change in WSS in 12 h	–2·52 (2·35); 232	–2·43 (2·46); 240	3 (472)	–0·02 (–0·17 to 0·14)†	0·68	0·0%	<0·001
Length of hospital stay, h	18·0 (26·0); 731	21·9 (28·0); 721	5 (1452)	–3·18 (–4·43 to –1·93)†	0·0021	0·0%	<0·001
Revisit to general practice or emergency department	189/779 (24·3%)	185/819 (22·6%)	7 (1598)	1·11 (0·86 to 1·43)*	0·35	0·0%	<0·001
Rehospitalisation	51/701 (7·3%)	49/705 (7·0%)	5 (1406)	0·94 (0·38 to 2·32)*	0·87	36·2%	0·21
Need for additional steroids	40/724 (5·5%)	59/756 (7·8%)	7 (1480)	0·71 (0·39 to 1·28)*	0·20	0·0%	0·053
Time back to normal, days	4·56 (3·92); 451	5·04 (4·13); 469	5 (920)	–0·64 (–1·76 to 0·49)†	0·19	58·9%	0·31
Doses of short-acting β_2 agonist in 7 days	19·05 (28·42); 210	22·44 (38·15); 236	2 (446)	0·34 (–7·09 to 7·76)†	0·67	0·0%	<0·001
Doses of short-acting β_2 agonist in 14 days	31·02 (47·12); 136	39·26 (62·30); 153	2 (289)	–4·75 (–6·71 to –2·79)†	0·021	0·0%	<0·001

Outcome data are mean (SD); n or n/N (%) , unless otherwise specified. All analyses were done by a two-stage approach. All models were adjusted for age, combined personal allergies (eczema, hay fever, or food allergy) and combined parental allergies (eczema, hay fever, or food allergy) or parental asthma. WSS=wheezing severity score. *Odds ratio (binary outcomes). †Mean difference (continuous outcomes).

Table 2: **Primary and secondary outcomes among studies included in the individual participant data meta-analysis**

For length of hospital stay, there was a significant reduction in the oral corticosteroids group compared with placebo (mean difference –3·18 h [95% CI –4·43 to –1·93]; p=0·0021; 1452 children in five studies).[7,10,19,27,29] In a sensitivity analysis, we could not integrate the aggregate estimate of length of hospital stay from the WASP study[11] due to incompatible calculations of differences. However, their reported median difference in inpatient length of hospital stay (–2·9 h [–7·8 to 2·4]) was similar to our estimate, albeit with a wider 95% CI.

We found no evidence of benefit of oral corticosteroids when compared with placebo for long-term outcomes: revisit to general practice or emergency department, rehospitalisation, need for additional steroids, and time back to normal (table 2). A significant reduction in doses of short-acting β_2 agonist in 14 days was observed across two studies from a single site recruiting 289 children exclusively with recurrent wheeze, with very low-quality evidence for this measure (–4·75 [–6·71 to –2·79]; p=0·021).[19,28] Sensitivity analyses for all outcomes were consistent with the results (appendix pp 18–20).

Prespecified subgroup analyses were conducted to identify the effect of modifiers (figure 2, figure 3; appendix pp 29–35). Baseline moderate-to-severe wheeze was associated with an absolute decrease (indicating improvement) in change in WSS at 4 h in the oral corticosteroids group compared with the placebo group (mean difference –0·38 [95% CI –0·40 to –0·37]) with no significant change observed in those with mild wheeze (–0·07 [–1·41 to 1·28]). The interaction was not statistically significant ($p_{interaction}$ =0·28; figure 2). There was no evidence of a significant change in either group at 12 h (appendix p 29). Other factors, including age (12–35 months or 36–71 months), male sex, allergies, and parental allergies or asthma did not modify the effects of oral corticosteroids.

For length of hospital stay, baseline wheezing severity and a history of wheezing or asthma were associated with a greater magnitude of effect of oral corticosteroids (figure 3). Subgroup analyses showed that oral corticosteroids were associated with a significantly greater reduction in length of hospital stay in children presenting with a history of wheezing or asthma (mean difference –4·54 h [95% CI –5·57 to –3·52]; $p_{interaction}$=0·0007) or with moderate-to-severe wheeze (–3·38 h [–6·10 to –0·67]; $p_{interaction}$<0·001). No evidence of differential effects of oral corticosteroids was seen between children with or without allergies or parental history of allergies or asthma, or between males and females. Providing oral corticosteroids in emergency departments was associated with a greater reduction in length of hospital stay (–3·28 h [–4·30 to –2·26]) and the need for additional steroids (OR 0·53 [95% CI 0·30 to 0·95]) than was providing oral corticosteroids in inpatient settings (mean difference –2·50 [–30·71 to 25·71]; OR 0·82 [0·28 to 2·40]; appendix p 21). For long-term outcomes, including revisit to general practice or emergency department, rehospitalisation, the need for additional steroids, the time back to normal, and doses of short-acting β_2 agonist, effects of oral corticosteroids did not statistically differ between those with and without any risk factors (appendix pp 30–35).

Due to potential differentiating effects by baseline WSS, we performed a post-hoc analysis for additional demographic characteristics of participants with mild wheeze and with moderate-to-severe wheeze. The moderate-to-severe wheeze group had a significantly higher proportion of children with a history of allergies and parental eczema or asthma compared with the mild group (appendix p 22; all p<0·05). After adjusting for other risk factors to confirm the effect modification of baseline WSS, significant effects of oral corticosteroids on length of hospital stay were observed in the moderate-to-severe

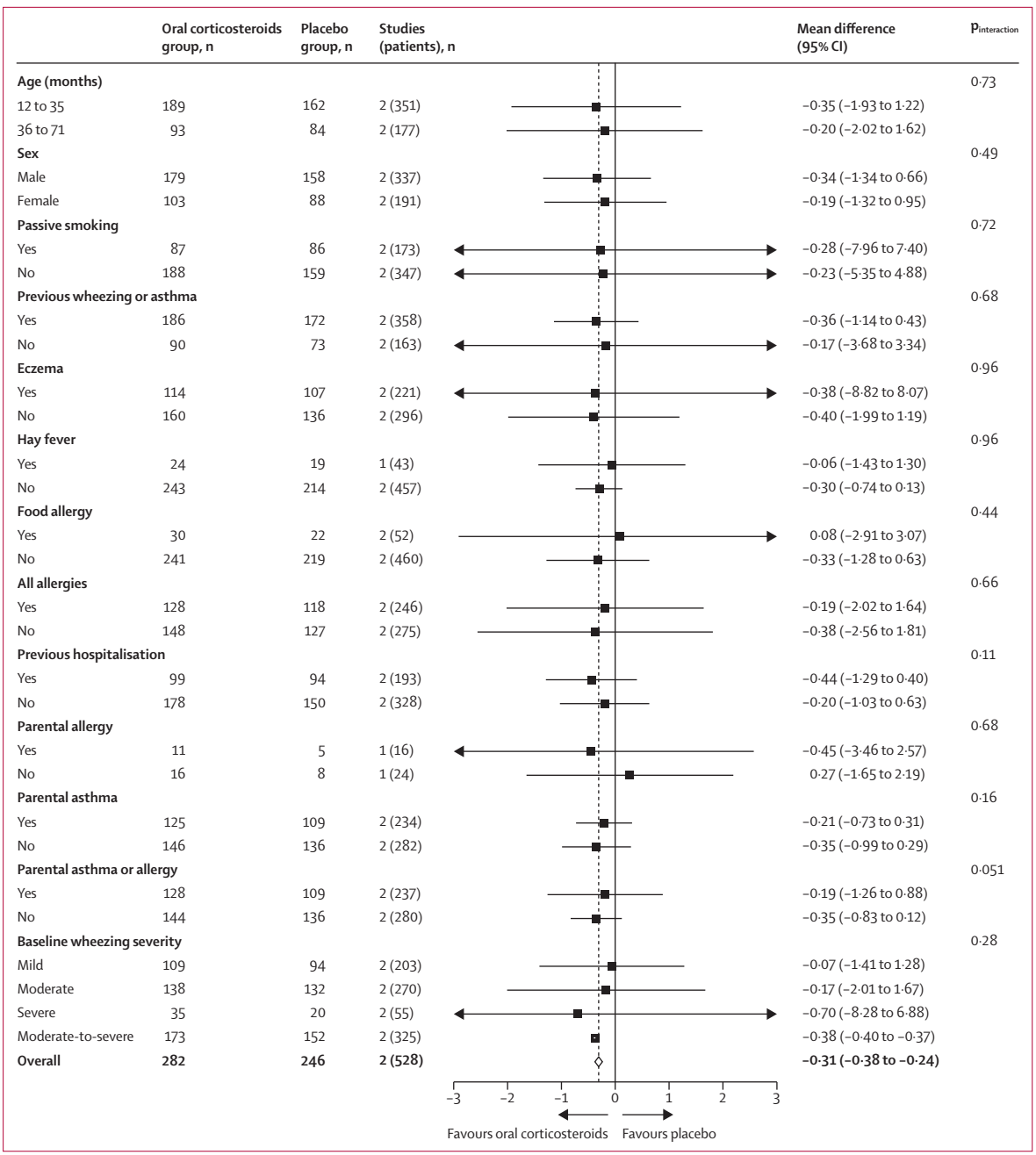

Figure 2: **Two-stage individual participant data meta-analysis for change in wheezing severity score at 4 h by subgroups**

wheeze group (mean difference −3·10 [95% CI −5·27 to −0·92]), but not in the mild wheeze group (−2·23 [−6·64 to 2·18]; $p_{interaction}$=0·0004; table 3). Compared with placebo, children given oral corticosteroids in the moderate-to-severe wheeze group showed more improvement in baseline severity within 4 h (−0·39 [−0·73 to −0·06]) than did those in the mild wheeze group (−0·07 [−2·04 to 1·89]). A higher risk of rehospitalisation was observed in the mild group (OR 1·47 (0·13 to 17·14)) compared with the moderate-to-severe wheeze group (OR 1·25 (1·16 to 1·35)), although the absolute difference in risk was very small, possibly resulting from too few observations with a non-significant interaction. Due to limitations in available data, a meta-analysis for short-acting β_2 agonist doses in 7 days and 14 days was not feasible. Consequently, each model incorporated only one study.[7,19] The analyses showed no overall effects in either the mild wheeze or the moderate-to-severe wheeze group for both follow-up periods, but significant crossover interactions were observed.

	Oral corticosteroids, mean (SD)	Oral corticosteroids group, n	Placebo, mean (SD)	Placebo group, n	Studies (patients), n	Mean difference (95% CI)	$P_{interaction}$
Age (months)							0·60
12 to 35	21·59 (30·52)	399	25·81 (30·10)	385	3 (784)	−3·18 (−5·72 to −0·63)	
36 to 71	12·10 (13·94)	275	15·53 (22·77)	275	3 (550)	−3·32 (−10·54 to 3·90)	
Sex							0·28
Male	17·57 (26·56)	463	22·28 (29·09)	469	4 (932)	−4·21 (−6·60 to −1·82)	
Female	18·66 (25·67)	252	21·05 (26·58)	235	4 (487)	−2·20 (−4·68 to 0·28)	
Passive smoking							0·81
Yes	18·64 (27·84)	247	23·79 (28·74)	250	5 (497)	−2·73 (−5·53 to 0·07)	
No	17·09 (24·28)	469	20·39 (26·73)	463	5 (932)	−2·95 (−5·48 to −0·43)	
Previous wheezing or asthma							0·0007
Yes	15·68 (24·36)	415	20·33 (28·76)	420	3 (835)	−4·54 (−5·57 to −3·52)	
No	18·49 (28·01)	195	20·31 (26·76)	181	3 (376)	−0·13 (−1·30 to 1·04)	
Eczema							0·37
Yes	19·45 (27·54)	267	22·74 (26·49)	296	5 (563)	−3·96 (−5·35 to −2·57)	
No	16·91 (25·25)	448	20·90 (28·39)	416	5 (864)	−2·67 (−4·66 to −0·68)	
Hay fever							0·19
Yes	13·61 (14·26)	52	19·10 (20·08)	63	3 (115)	−6·73 (−12·80 to −0·65)	
No	14·39 (19·62)	601	17·61 (22·83)	577	3 (1178)	−2·93 (−4·02 to −1·83)	
Food allergy							0·80
Yes	23·27 (31·08)	120	26·39 (27·10)	137	5 (257)	−3·44 (−6·66 to −0·22)	
No	16·86 (25·02)	592	20·52 (27·72)	569	5 (1161)	−3·01 (−5·18 to −0·83)	
All allergies							0·31
Yes	18·47 (25·79)	326	22·07 (25·18)	357	5 (683)	−4·08 (−5·47 to −2·70)	
No	17·50 (26·42)	395	21·34 (29·81)	359	5 (754)	−2·44 (−5·01 to 0·13)	
Previous hospitalisation							0·66
Yes	13·99 (19·66)	291	18·33 (23·60)	306	4 (597)	−2·84 (−5·64 to −0·04)	
No	20·75 (30·61)	391	24·03 (31·80)	352	4 (743)	−3·20 (−3·78 to −2·61)	
Parental allergy							0·16
Yes	19·97 (29·41)	212	22·59 (29·57)	211	3 (423)	−4·57 (−7·00 to −1·75)	
No	17·25 (28·73)	206	24·04 (31·99)	199	3 (405)	−1·82 (−3·91 to 0·26)	
Parental asthma							0·21
Yes	13·96 (20·42)	329	18·74 (25·47)	325	5 (654)	−4·22 (−7·43 to −1·00)	
No	20·94 (29·13)	377	24·35 (29·26)	374	5 (751)	−1·40 (−3·18 to 0·38)	
Parental asthma or allergy							0·17
Yes	17·01 (24·35)	412	20·61 (26·48)	395	4 (807)	−3·90 (−5·07 to −2·73)	
No	18·58 (28·14)	280	23·18 (29·82)	289	4 (569)	−1·57 (−3·50 to 0·36)	
Baseline wheezing severity							<0·001
Mild	7·30 (8·69)	298	10·45 (20·93)	170	3 (468)	−3·08 (−7·66 to 1·49)	
Moderate	20·07 (24·60)	274	20·88 (20·90)	288	3 (562)	−1·99 (−7·62 to 3·63)	
Severe	20·64 (17·90)	98	29·03 (24·35)	99	3 (197)	−6·69 (−15·14 to 1·77)	
Moderate-to-severe	20·22 (23·00)	372	22·97 (22·09)	387	3 (759)	−3·38 (−6·10 to −0·67)	
Overall	**18·00 (26·00)**	**731**	**21·90 (28·00)**	**721**	**5 (1452)**	**−3·18 (−4·43 to −1·93)**	

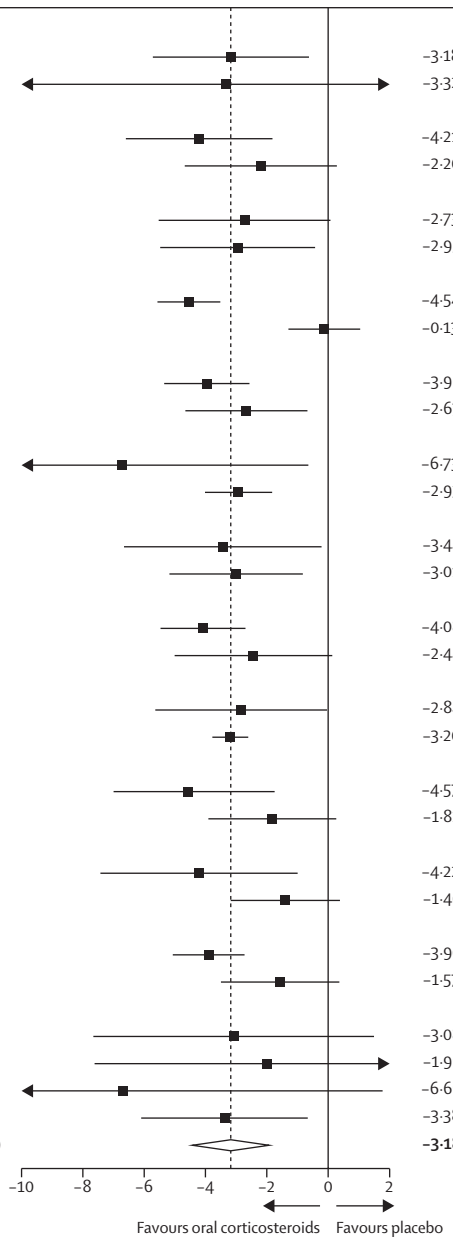

Figure 3: **Two-stage individual participant data meta-analysis for effects of oral corticosteroids on length of hospital stay (in hours) by subgroups**

The associations between oral corticosteroids and six commonly reported adverse events (diarrhoea, vomiting, agitation, stomach ache, nausea, and stomach upset) were investigated (appendix p 23). The incidence of adverse events was very low, suggesting that oral corticosteroids were well tolerated. However, there was a higher risk of vomiting associated with oral corticosteroids than with placebo (22 [4·5%] of 492 *vs* 11 [2·2%] of 495 children from four studies; OR 2·27 [95% CI 0·87 to 5·88]; $\tau^2<0·001$). The quality of evidence is detailed in the appendix (pp 24–25). High-quality evidence supports outcomes such as WSS change at 12 h, length of hospital stay, revisit to general practice or emergency department, rehospitalisation, and the need for additional steroids. Moderate-quality evidence was determined for the time back to normal and WSS change at 4 h, whereas evidence for doses of short-acting β_2 agonist was very low quality.

	Oral corticosteroids group	Placebo group	Studies (patients), n	Combined odds ratio* or mean difference† (95% CI)	p value	$p_{interaction}$	I^2	τ^2
Change in WSS in 4 h, n	282	246	..	..	..	..	..	..
Mild wheeze	−0·81 (1·32)	−0·72 (1·50)	2 (203)	−0·07 (−2·04 to 1·89)†	0·72	0·23	0·0%	<0·001
Moderate-to-severe wheeze	−2·66 (2·27)	−2·19 (2·10)	2 (325)	−0·39 (−0·73 to −0·06)†	0·042	..	0·0%	<0·001
Change in WSS in 12 h, n	232	240	..	..	..	..	..	..
Mild wheeze	−0·69 (1·46)	−0·54 (1·85)	3 (83)	−0·42 (−2·01 to 1·17)†	0·37	0·34	21·6%	<0·001
Moderate-to-severe wheeze	−2·92 (2·32)	−2·81 (2·39)	3 (389)	−0·01 (−0·72 to 0·70)†	0·96	..	0·0	<0·001
Length of stay, h	686	674	..	..	..	..	..	..
Mild wheeze	7·39 (8·68)	10·46 (20·81)	4 (575)	−2·23 (−6·64 to 2·18)†	0·21	0·0004	17·3%	2·00
Moderate-to-severe wheeze	20·32 (22·68)	23·04 (21·77)	4 (785)	−3·10 (−5·27 to −0·92)†	0·020	..	0·0%	<0·001
Revisit to general practice or emergency department, n	533	531	..	..	..	..	..	..
Mild wheeze	59/271 (21·8%)	53/253 (20·9%)	2 (524)	1·04 (0·02 to 46·12)*	0·91	0·64	41·1%	0·080
Moderate-to-severe wheeze	66/262 (25·2%)	66/278 (23·7%)	2 (540)	1·05 (0·33 to 3·40)*	0·67	..	0·0%	<0·001
Rehospitalisation, n	533	531	..	..	..	..	..	..
Mild wheeze	24/271 (8·9%)	16/253 (6·3%)	2 (524)	1·47 (0·13 to 17·14)*	0·30	0·43	0·0%	<0·001
Moderate-to-severe wheeze	17/262 (6·5%)	14/278 (5·0%)	2 (540)	1·25 (1·16 to 1·35)*	0·017	..	0·0%	<0·001
Additional steroids, n	515	514	..	..	..	..	..	..
Mild wheeze	8/251 (3·2%)	9/236 (3·8%)	3 (487)	0·90 (0·20 to 4·11)*	0·79	0·32	0·0%	<0·001
Moderate-to-severe wheeze	17/264 (6·4%)	30/278 (10·8%)	3 (542)	0·51 (0·03 to 8·13)*	0·41	..	48·1%	0·41
Time back to normal, days	327	335	..	..	..	..	..	..
Mild wheeze	5·00 (3·59)	5·66 (4·86)	3 (191)	−2·58 (−13·43 to 8·27)†	0·41	0·72	92·9%	17·37
Moderate-to-severe wheeze	5·39 (4·17)	5·65 (4·20)	3 (471)	−0·74 (−4·35 to 2·88)†	0·47	..	69·3%	1·37
Doses of short-acting β_2 agonist in 7 days, n	160	168	..	..	..	..	..	..
Mild wheeze	8·77 (6·03)	9·61 (6·22)	1 (127)	−0·65 (−2·81 to 1·51)†	0·56	0·0033	NA	NA
Moderate-to-severe wheeze	10·75 (9·02)	9·71 (8·26)	1 (201)	1·17 (−1·23 to 3·58)†	0·34	..	NA	NA
Doses of short-acting β_2 agonist in 14 days, n	86	86	..	..	..	..	..	..
Mild wheeze	18·43 (13·26)	10·50 (12·02)	1 (9)	6·08 (−16·59 to 28·76)†	0·63	0·010	NA	NA
Moderate-to-severe wheeze	15·01 (16·44)	20·01 (16·92)	1 (163)	−5·25 (−10·52 to 0·01)†	0·052	..	NA	NA

Outcome data are n, mean (SD), or n/N (%), unless otherwise specified. All analyses were done by a two-stage approach. All models were adjusted for age, combined personal allergies (eczema, hay fever, or food allergy) and combined parental allergies (eczema, hay fever, or food allergy) or parental asthma. NA=not applicable *Odds ratio (binary outcomes). †Mean difference (continuous outcomes).

Table 3: **Subgroup analyses for primary and secondary outcomes by mild versus moderate-to-severe wheeze at baseline**

Discussion

In this systematic review, our conventional aggregated meta-analyses were unable to provide appropriate estimates of effect due to the distribution of included age ranges and incompatible statistical metrics. However, our IPD meta-analysis enabled us to show that children with acute preschool wheeze who received oral corticosteroids had statistically significant improvement in WSS at 4 h and length of hospital stay. The effect of oral corticosteroids on these outcomes was greater in children presenting with moderate-to-severe wheeze than in those presenting with mild wheeze. Administration of oral corticosteroids in the emergency department (*vs* inpatient) was also associated with improved length of hospital stay. However, the greatest reduction in length of hospital stay was found in children with a history of previous wheeze or asthma. Other risk factors such as personal allergies or parental allergies or parental asthma did not improve outcomes. However, care should be taken not to overinterpret these findings due to multiple testing of subgroups effects. Reported adverse events were infrequent, although oral corticosteroids were associated with a higher risk of vomiting. To date, trials have had limited ability to consistently demonstrate these outcomes due to limited power, as either there is a substantial proportion of children presenting with milder symptoms or there are small proportions who have previous wheeze or asthma.

The significant improvement in WSS observed at 4 h was not observed at 12 h. Although more studies contributed to the 12 h observation, there were fewer participants (528 *vs* 472) available for analyses as many were discharged from care by 12 h. Many children with acute wheeze have recovered sufficiently to be discharged from acute care by 12 h (median placebo time to discharge 9·0 h in PREVIEW and 13·9 h in Panickar).[7,10] Although the differential at 12 h continued to be positive for oral

corticosteroids compared with placebo, the convergence of populations towards recovery at this timepoint limited the opportunity to observe any meaningful difference.

Globally, guidelines provide recommendations that are frequently risk–benefit based. The conflicting evidence surrounding oral corticosteroids is considered with recognition of the clinical tension that both no treatment and treatment adverse effects carry potential risk. Current guideline recommendations for oral corticosteroid treatment in acute preschool wheeze vary (appendix p 4). Our data support the risk–benefit approach adopted by guidelines for those presenting with moderate-to-severe wheeze. A reduction in WSS at 4 h was accompanied by a modest improvement in length of hospital stay. In addition, providing oral corticosteroids in the emergency department had a greater effect on the length of hospital stay than did providing oral corticosteroids as an inpatient. These early effects are consistent with the pharmacokinetics of prednisolone, which reaches peak plasma concentrations between 0·5 to 3·0 h after administration and has a half-life ranging from 2·1 to 3·5 h.[31] On the basis of these data, we advocate that those with moderate-to-severe wheeze presenting to the emergency department be provided with oral corticosteroids, a suggestion that encompasses and refines current guideline recommendations.

However, implementing recommendations based on acute wheeze severity is difficult, as wheeze severity scores are inadequately integrated into clinical care.[32] The validated PRAM score is most widely used as a research tool and can predict hospital admission from the emergency department if used at 3 h after presentation.[33] However, PRAM has low discriminatory ability between levels of asthma severity[34] and is inconsistent when evaluating dyspnoea.[35] Similarly to most asthma scores, PRAM incorporates subjective categorisation of continuous clinical signs (eg, work of breathing) that can deliver inconsistent interpretation. Research to develop a clinically simple scoring tool that demonstrates good validity and severity discriminatory ability in preschool children would be of value in integrating the output of this IPD meta-analysis into clinical care. Understanding and resolving perceived barriers to clinical integration would also be vital to implementation.

Identifying patient characteristics that could help to reduce oral corticosteroid exposure in those who are least likely to respond is a high clinical priority. Our data support a clinically relevant improvement in length of hospital stay when oral corticosteroids are provided to those with previous wheeze or asthma. This order of improvement is consistent with a 5 h median acute preschool wheeze oral corticosteroid treatment minimal clinically important difference for reduction in length of hospital stay reported from an international survey of clinicians.[36] A 4·54 h reduction in length of hospital stay could affect patient management by reducing the need for admission to hospital or by enabling earlier discharge home. Targeting oral corticosteroids to those children with acute preschool wheeze presenting with a previous history of wheeze or asthma could be clinically implementable immediately. Future research might help to deliver better stratification of acute preschool wheeze endotypes (eg, biomarkers such as eosinophils)[37] that could further help to reduce oral corticosteroid exposure in patients who are least likely to respond.

In clinical practice, the decision to treat acute preschool wheeze with oral corticosteroids is influenced by a child's age.[14] This influence of age has been presumed based on a graded extrapolation of strong evidence showing the lack of benefit in children younger than 1 year with acute bronchiolitis and showing benefit in those with asthma from age 6 years or older. An increasing proportion of children with acute wheeze develop asthma between age 1 year and 6 years during this period[38] and a third will have a diagnosis of asthma at age 6–8 years.[39] However, we found no evidence to support a differential response to oral corticosteroids based on age (12 to 35 months or 36 to 71 months).

The adverse effects of oral corticosteroids, particularly with repeated use, are a frequent concern in acute preschool wheeze. There were few and generally mild adverse events with single courses of steroids, where recorded in the included trials (appendix p 23), consistent with a previous systematic review.[40] None of the included studies examined adverse events associated with repeated corticosteroid prescriptions (eg, future fracture risk), which is an area future studies should explore.

This study has several strengths. Our exhaustive systematic searches ensured the inclusion of all relevant and large-scale studies and helped to include (seven) more recent studies published since 2000, reducing the risk of publication bias compared with a previous review (two published since 2000).[6] Using IPD has enhanced the robustness of our results by increasing the information size, which a conventional meta-analysis could not achieve, subsequently improving the statistical power. Furthermore, we minimised selection bias, attribution bias, and outcome reporting bias by conducting an intention-to-treat analysis and standardising eligibility criteria, outcome measures, and statistical models across the studies. By determining the primary outcome via a consensus meeting with stakeholders, we ensured our meta-analysis provided practical evidence highly relevant to both caregivers and clinicians.

There were also limitations. Although we applied standardised eligibility criteria, the definition of acute preschool wheeze varied among the included studies. Of the seven datasets, three confirmed viral wheezing using viral testing data,[10,19,29] whereas four reported viral wheezing using clinical symptoms and signs of a viral infection.[7,27,28,30] To confirm the presence of allergies, three studies checked allergen-specific IgE antibody

concentrations,[19,29,30] but others relied on questionnaires completed by a parent or guardian. Consequently, our evidence provides clinical recommendations about oral corticosteroids for a broad interpretation of acute preschool wheeze. Improvement in WSS was the preferred primary outcome for oral corticosteroid treatment in this population by our stakeholders. However, this outcome was only recorded in four studies (one study at 4 h and 12 h, one study at 4 h, and two studies at 12 h). The significant change in WSS observed at 4 h was aligned with an improved score at the same timepoint in the WASP trial.[11] Although IPD meta-analysis is the best way to standardise baseline characteristics and statistical approaches across studies, we could not address variations in data recording methods affecting variable quality and analysis results. We mitigated this limitation by merging similar variables, restricting a full review of all covariates in each trial. Some analyses were also limited by the level of detail recorded for outcomes, in which proportion at a threshold time (eg, 7 or 14 days) was more commonly recorded than time to event (on a continuous scale). Prednisolone was used in all included studies at various dose–duration combinations, making a comparative analysis too complex (appendix p 25). Although two randomised controlled trials have shown no significant differences in the proportion of children who were symptom free, in quality of life, or in the change in PRAM score for duration (3 *vs* 5 days) or dose (a 3-day course of 1 mg/kg *vs* 2 mg/kg)[41,42] of prednisolone, future studies should explore optimal dose and duration.

In conclusion, this study provides reliable evidence and demonstrates early benefits of oral corticosteroids, increasing in those with moderate-to-severe wheeze. In children with a history of previous wheeze or asthma, the significant improvement in length of hospital stay with oral corticosteroids was similar to a previously reported minimal clinically important difference. Participants with mild wheeze or no previous wheeze history presenting to the emergency department could be provided with safe-guarding information without initiating oral corticosteroids at that time. Evidence for oral corticosteroid use in a community setting was too limited to draw conclusions. Adverse effects were few and mild, although there was an increased risk of vomiting associated with oral corticosteroids. Oral corticosteroids appear to have no benefit for long-term outcomes, including the need for additional asthma medication or health-care service revisits.

Contributors

BL, ST, SL, and SC conceived the study and wrote the initial protocol and the manuscript. BL and JT-P did the systematic review. PC, AO, TJ, MB, JG, and TWG helped prioritise outcome measures before the analysis and shared trial data and gave feedback on the protocol. ST, SL, and SC guided the statistical analysis. BL, SL, and SC accessed and verified all the data in the study and conducted the analyses. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

The study protocol (R script) for the IPD meta-analysis is available on request from the corresponding author. The data used in this study are individual participant-level data, which are regulated by local ethics committees and cannot be shared.

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