FIGURES

Figure 1. Flow diagram

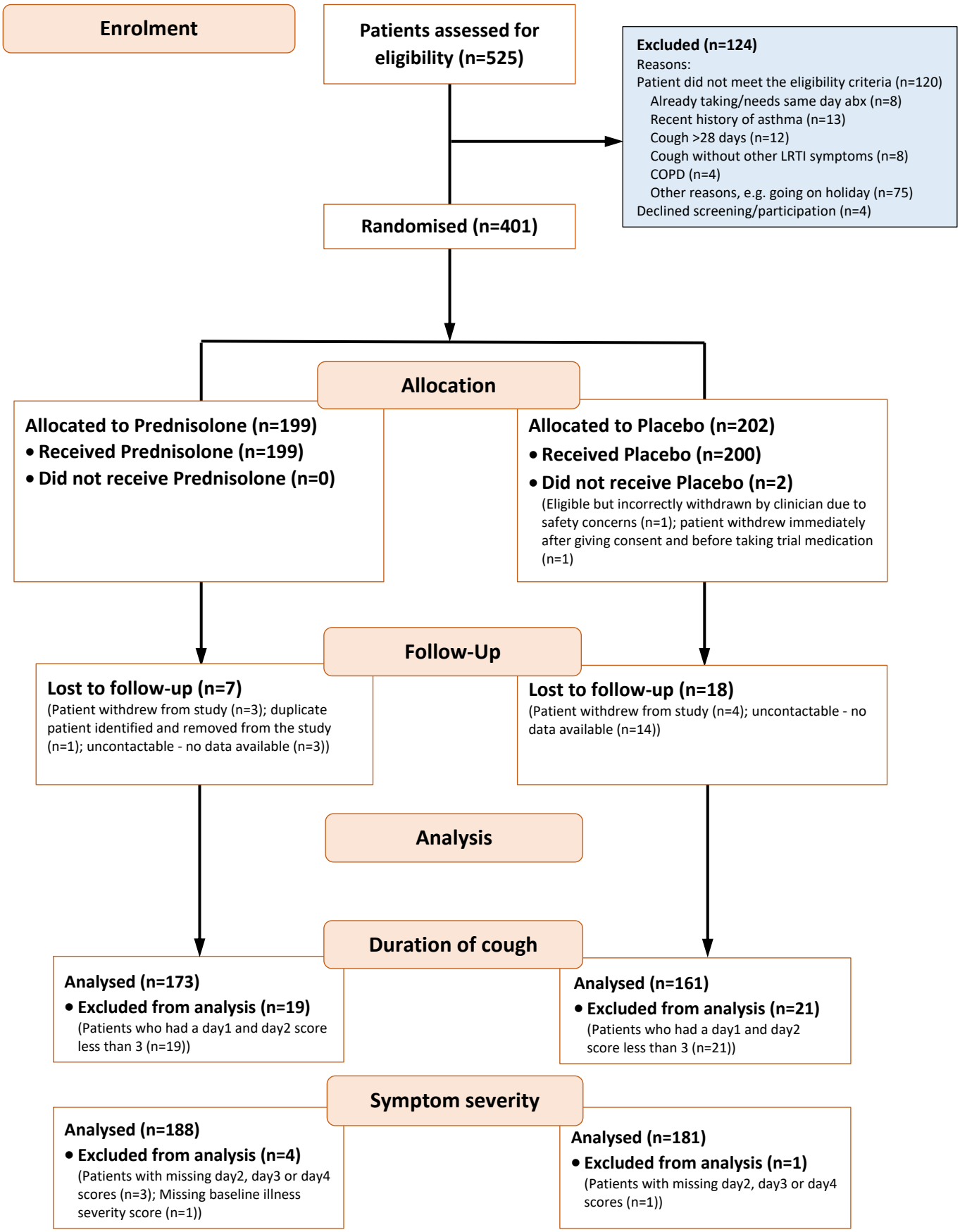
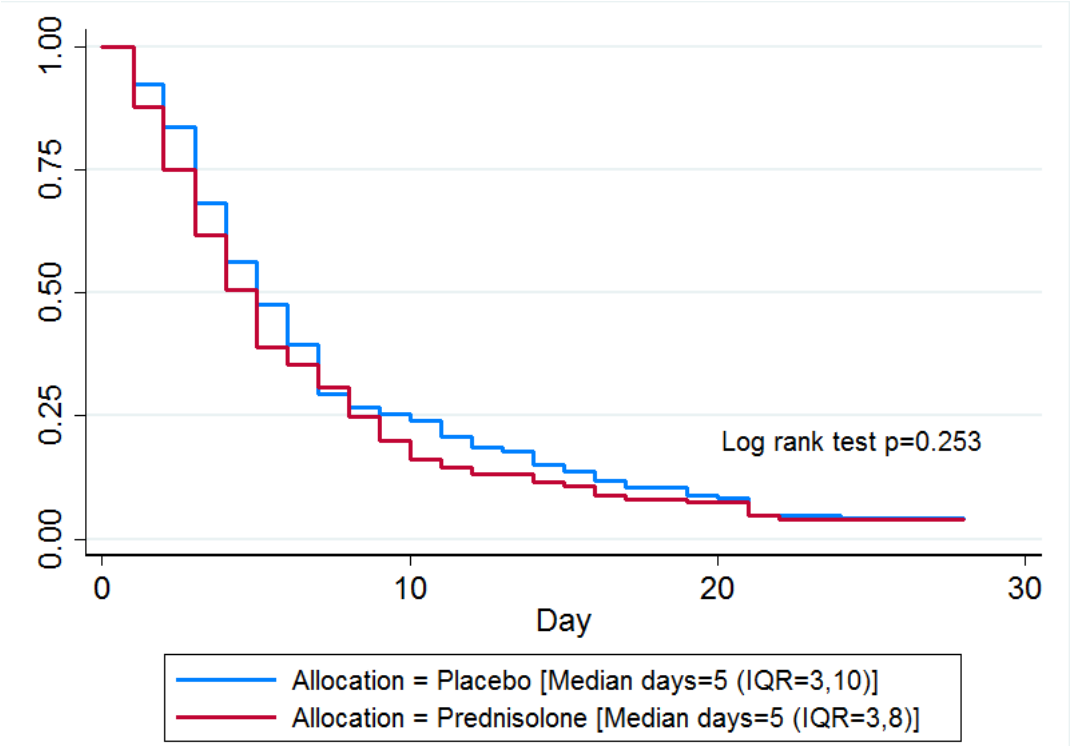


Figure 2. Kaplan Meier curve for time to recovery from moderately bad or worse cough



Number at risk (those left to recover)																												
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Placebo	161	149	135	109	90	76	63	44	40	38	35	30	27	26	22	20	17	15	15	13	12	7	7	7	6	6	6	5
Prednisolone	173	152	129	106	87	66	60	51	41	33	27	24	22	22	17	16	13	12	12	11	11	7	6	6	6	5	5	5

Effect of oral prednisolone on symptom duration in non-asthmatic adults with acute lower respiratory tract infection: a randomized clinical trial

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Keywords

Respiratory tract infections, prednisolone, randomized controlled trials, primary health care

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KEY POINTS

Question: Does a moderate dose of oral corticosteroid reduce the duration or severity of acute lower respiratory tract infection in non-asthmatic adults presenting to primary care?

Findings: In this randomized trial of 401 adults with symptoms of acute lower respiratory tract infection, treatment with oral prednisolone 40 mg daily for 5 days compared with placebo did not significantly reduce the median duration of moderately bad or worse cough (5 days in each group) or the mean severity of symptoms between days 2 and 4 (1.99 vs 2.16 points out of 6)..

Meaning: These findings do not support the use of oral steroids for the treatment of acute lower respiratory tract infection in the absence of asthma.

ABSTRACT

Importance: Acute lower respiratory tract infection is common and often treated inappropriately in primary care with antibiotics. Corticosteroids are increasingly used but without sufficient evidence.

Objective: To assess the effects of oral corticosteroids for acute lower respiratory tract infection in non-asthmatic adults.

Design, setting and participants: Multicenter, placebo controlled, randomized trial (July 2013 to final follow-up October 2014) in 54 family practices in England. 401 adults with acute cough and at least one lower respiratory tract symptom, not requiring immediate antibiotic treatment and no history of chronic pulmonary disease or use of asthma medication in past 5 years. Two immediately withdrew, one duplicate patient was identified.

Intervention: Two 20mg prednisone tablets (n=198) or matched placebo (n=200) once daily for 5 days.

Main outcomes and measures: Primary - duration of moderately bad or worse cough (0 to 28 days; minimal clinically important difference 3.79 days) and mean symptoms' severity on days 2 to 4 (scored from 0 (not affected) to 6 (as bad as it could be); minimal clinically important difference 1.66 units). Secondary - duration and severity of acute lower respiratory tract infection symptoms; duration of abnormal peak flow; antibiotic consumption; adverse events.

Results: Among 398 patients with baseline data (mean age 47 (SD 16.0); 63% female; 17% smokers; 77% phlegm; 70% shortness of breath; 47% wheezing; 46% chest pain; 42% abnormal peak flow): 334 (84%) provided cough duration and 369 (93%) symptoms' severity. Median cough duration was 5 days (IQR, 3-8) in the prednisolone group and 5 days (IQR, 3-10) in the placebo group, adjusted HR 1.11 (95% CI 0.89 to 1.39, P=0.36, alpha 0.05). Mean symptoms' severities were 1.99 and 2.16, adjusted difference -0.20 (95% CI -0.40 to 0.00, P=0.05, alpha 0.001). No significant treatment effects were observed for duration or severity of acute lower respiratory tract infection symptoms, duration of abnormal peak flow, antibiotic consumption or non-serious adverse events. There were no serious adverse events.

Conclusions and relevance: Oral corticosteroids should not be used for acute lower respiratory tract infection symptoms in adults without asthma as they do not reduce symptom duration or severity.

Trial registration: ISRCTN57309858.

Words: 350

INTRODUCTION

Acute lower respiratory tract infection (ALRTI), defined as an acute cough with at least one of sputum, chest pain, shortness of breath and/or wheeze,[1] is one of the most common conditions managed in primary care internationally. In 2009 to 2011, an estimated 65% to 75%[2,3] of patients were prescribed antibiotics, despite good evidence they do not reduce symptom duration or severity,[4] and guidelines to the contrary.[1] Annual antibiotic prescribing costs are estimated at US$726 million in the US,[5] and US$300 million for consultations and antibiotics in the UK.[6]

Antimicrobial resistance (AMR) is one of the greatest challenges to modern public health.[7] Primary care is responsible for 80% of health service antibiotic prescribing,[2,8] with a high proportion regarded as unnecessary[2] and contributing to AMR.[9] Both US[10] and UK[11] national AMR action plans recommend finding alternatives to antibiotics, but none is currently proven for ALRTI in adults.

Symptoms of ALRTI are similar to those of exacerbated asthma.[12] Bronchial epithelial changes are similar in people with and without asthma during a RTI, with both groups showing reductions in forced expiratory volume and airways inflammation,[12] and prolonged ALRTI symptoms are thought to be due to bronchial hyper-responsiveness.[13] Oral and inhaled corticosteroids are highly effective for acute asthma, but US, British and European guidelines do not provide guidance on whether corticosteroids should be used for ALRTI. Despite this, US and European clinicians are increasingly using oral and inhaled steroids, with one US study[14] reporting oral prednisolone use in 15% of non-asthmatic adults with ALRTI.

A previous systematic review[15] found insufficient evidence regarding the role of inhaled corticosteroids and found no oral corticosteroid studies for ALRTI. The aim of this study was to investigate the effects of a moderate dose of oral corticosteroids in non-asthmatic adults presenting to primary care with ALRTI.

METHODS

Ethical approval, consent, study design, participant recruitment and baseline assessment

Ethical approval was granted by the Central Bristol Research Ethics Committee (12/SW/0180) and all patients gave informed, written consent. The Oral Steroids for Acute Cough (OSAC) trial was a multicenter, placebo-controlled, individually randomized study, conducted between July 2013 and October 2014. Family physicians and nurses ('recruiting clinicians') were trained in study procedures by four centers at the Universities of Bristol, Southampton, Nottingham and Oxford. They were asked to assess eligibility in consecutive patients: aged ≥18 years; consulting for an acute (≤28 days) cough as the main symptom with at least one lower respiratory tract symptom (phlegm, chest pain, wheezing or shortness of breath) in the previous 24 hours. Patients were excluded if they: were clinically suspected to have, or their medical records showed evidence of, chronic pulmonary disease; had received any asthma medication in the past 5 years; met NICE criteria for severe infection/complications;[1] required same-day hospital admission; or required same day antibiotics (see Online Supplement for full list). Participants were recruited on the day of, or the day following, presentation. Following consent, demographic and clinical data were collected, including self-reported ethnicity using UK approved[16] categories, to assess sample representativeness.

Randomization and concealment

The treatment allocation schedule was computer-generated by a statistician independent of the trial team. Randomization (1:1 ratio prednisolone:placebo) used a variable block size (4, 6, 8 and 10) and was stratified by center. Allocated medication was added to numbered participant packs by pharmacists, independent of the team. All packs were identical and centers distributed four packs to family practices at a time. Following eligibility confirmation, participants were given the next pack.

Intervention and masking

Participant packs contained either 10 prednisolone 20 mg oral tablets (procured GALEN Pharma GmbH, Germany) or matched (dimension, appearance and taste) placebo tablets (Piramal Healthcare Ltd, UK). Participants were asked to take two tablets once daily for five days, starting on the day of consultation, if possible before starting any antibiotics (if receiving a 'delayed' prescription). The dose and duration of prednisolone was selected to reflect the dose and duration known to be effective for acute asthma.[17] Participants, recruiting clinicians and the trial team were masked to treatment allocation until data analyses were complete.

Follow up

Participants were invited to report (using web or paper versions) the presence and severity of symptoms using a validated[18] diary shown to be sensitive to change .[19] [4] Symptoms were measured using a scale from zero (no problem) to three (moderately bad) and up to six (as bad as it could be). All symptoms were

measured daily, with twice daily peak expiratory flow, for 28 days or until symptom resolution. Cough was measured for a further 28 days in case of late treatment effects. A research nurse telephoned participants weekly to support symptom diary completion. Participants were given £5 (US$6.6) shopping vouchers at 14 and 28 days. Medical notes were reviewed at 3 months for new diagnoses of asthma, COPD, whooping cough and lung cancer.

Primary outcomes

Two primary outcomes were used. The first was duration of moderately bad or worse cough, defined as the number of days from randomization to the last day scored ≥3, prior to at least two consecutive days scored <3, up to a maximum of 28 days. This was regarded as the more important of the two primary outcomes since cough was the main presenting symptom of the illness, and it included measures of both duration and severity. The second was the mean of the six main symptom (cough, phlegm, shortness of breath, sleep disturbance, feeling generally unwell, and activity disturbance) severity scores (each scored 0-6) on days 2 to 4; a mean score was calculated across the symptoms for each day and then an overall mean calculated, giving a maximum value of six.

Secondary outcomes

Secondary outcomes specified *a priori* were: total duration and severity of each symptom up to 28 days (cough, phlegm, shortness of breath, wheeze, blocked/runny nose, chest pain, fever, muscle aching, headache, sleep disturbance, feeling generally unwell, activity disturbance); duration of moderately bad/worse and any cough up to 56 days; duration of abnormal peak flow; antibiotic consumption; adverse events; re-consultation with evidence of illness deterioration; patient satisfaction with treatment; and intention to use the same treatment if it were to be available in the future (more detail about the derivation of these outcomes is provided in the Online Supplement). Quality of life, NHS treatment and investigation costs are not reported in this article.

Subgroup analyses

Pre-specified potential treatment effect modifiers were: age; prior cough duration; presence of wheeze; antibiotic consumption; b-agonist consumption; smoking status; history of hay fever, asthma or eczema; new diagnoses (at 3 months) of asthma, COPD, whooping cough or lung cancer. Baseline impression of severity of illness was added as a *post-hoc* sub group analysis as the trial team determined it was important to differentiate between those with severe vs. mild symptoms.

Sample size calculation

The distributions of both primary outcomes were expected to be positively skewed, hence sample size calculations were based on the log-normal distribution. The mean (standard deviation (SD)) duration of

moderately bad or worse cough and symptom severity score (days 2 to 4) were estimated as 5.8 (4.1) days and 2.3 (1.1) units respectively.[19] This corresponds to 1.56 (SD 0.64) log days (or geometric mean of 4.74 days) for cough duration and 0.73 (SD 0.45) units on the log scale (or geometric mean of 2.08) for symptom severity. As there were no previous studies of oral steroids to inform the minimum clinically important difference (MCID) in both outcomes, the investigative team considered the balance of potential benefits and adverse effects, and reached a MCID consensus of 20%, corresponding to a geometric mean in the active treatment group of 3.79 days (mean 1.33 log days) in terms of duration of cough and 1.66 units (mean 0.51 log units) for symptom severity. Allowing for 20% attrition, 218 participants needed to be randomized per group to retain 174 at follow-up and achieve 90% power with a two-sided alpha of 0.05 for primary outcome one. A final achieved sample size of 174 participants per group would provide 89% power to detect a 20% reduction in symptom severity, with an adjusted two-sided alpha of 0.001 to reflect its 'second primary outcome' status (see Online Supplement).

Statistical methods

Analysis of primary outcomes

A pre-specified analysis plan was approved by the Trial Steering and Data Monitoring Committees and the study protocol was published before data collection had finished (see Online Supplement). All analyses were performed in Stata 13.1.[20]

The primary comparative analyses considered patients in the groups to which they were randomized, without imputation for missing outcome data. These analyses were adjusted for center (Bristol, Nottingham, Oxford and Southampton), and the relevant baseline measure (prior cough duration (1-28 days) for duration of moderately bad or worse cough; patient reported illness severity in last 24 hours for symptom severity (0 completely well – 10 extremely unwell). Time-to-event methods were used to analyze the duration of moderately bad or worse cough. Semi-parametric Cox-proportional hazard models were employed (to enable comparison with previous studies) and the assumption of proportional hazards checked by visual inspection of the log-log survival curves and calculation of the Schoenfeld residuals.[21] Hazard ratios were reported comparing the instantaneous rate of resolution of cough between prednisolone and placebo groups, with 95% confidence intervals (CI) and P values. In order to assist interpretation against the MCID of a 20% reduction in time to resolution, for which hazard ratios are unhelpful, parametric Weibull Accelerated Failure Time (AFT) models were used to present cough duration treatment effects as time ratios. Such models can be formulated as proportional hazards or AFT models; hence hazard ratios were also produced from the Weibull models to ensure comparability with the Cox models.

Mean severity score from days 2 to 4 was considered in linear regression models. Models considered mean severity score and log mean severity score and distributional checks of residuals were undertaken to

determine the most appropriate model. Differences between the prednisolone and placebo groups are reported with 95% confidence intervals and P-values.

For both primary outcomes, secondary analyses additionally adjusted for factors demonstrating imbalance at baseline (a difference >5% for binary and >0.5SDs for continuous outcomes) and for smoking, since this is known to be prognostically important.[15]

Analysis of secondary outcomes, subgroup analyses and sensitivity analyses

Analyses of secondary outcomes used regression models as appropriate. Consideration of potential effect modifiers employed formal tests of interaction. Sensitivity analyses considered multiple imputation of missing data (using a two-fold fully conditional specification algorithm),[22 23] treatment adherence, day of recruitment, and inclusion of those with no moderately bad or worse cough at baseline (*post-hoc*). See Online Supplement for details.

RESULTS

Enrolment and study population

58 family physicians and 50 practice nurses based in 54 family practices assessed 525 patients for suitability, of whom 401 were eligible, consented and randomized: 199 to prednisolone and 202 to placebo (Figure 1), equating to a mean patient recruitment rate of 0.5 patients per month per practice. Two placebo group patients requested complete withdrawal immediately post randomization, and a further duplicate patient was subsequently identified in the prednisolone group (the participant remained in the group to which they were first allocated) leaving a sample of 398. The trial was stopped when the required number of participants was achieved. At baseline, participants had a mean age of 47.4 (SD 16.0) years; 37% were male; 3.5% had diabetes, 17% were currently smoking; 5% had received asthma medication more than 5 years previously; 77% reported phlegm; 46% chest pain; 47% wheezing; 70% shortness of breath; and 42% had abnormal (defined as <80% expected) peak flow. Baseline characteristics were similar between the groups with respect to deprivation, smoking status, weight, height and clinical characteristics of the ALRTI, though compared to placebo, the prednisolone group were slightly more likely to be male, older (and hence retired), and to have received an influenza vaccine in the last 12 months (Table 1).

Primary outcome data completeness

Symptom diaries were returned by 374 (94%) participants (192 prednisolone and 182 placebo). For duration of moderately bad or worse cough, data were available in 334 (84%) participants with 40 reporting an initial cough severity <3 (that is, not moderately bad or worse) and 24 lost to follow up. For symptom severity, follow-up data were available in 370 (93%). However, one participant in the prednisolone group had no baseline measure of illness severity and could not be used in the adjusted analysis. Patients who withdrew or were lost to follow up were younger (median 30 years vs. 49 years), less likely to be white (85% vs 97%), more likely to be employed (86% vs. 69%) and higher English Index of Multiple Deprivation score (18 vs. 11).

Primary analyses

Moderately bad or worse cough duration

The median duration of moderately bad or worse cough was 5 days (IQR, 3-8) in the prednisolone group and 5 days (IQR, 3-10) in the placebo group (Table 2). Kaplan Meier survival curves were similar for both groups (Figure 2). Visual inspection of the log-log survival curves and calculation of the Schoenfeld residuals (P=0.52) provided no evidence against proportional hazards. Comparing prednisolone with placebo, the Cox model adjusting for center and baseline cough duration resulted in a hazard ratio of 1.11 (95% CI 0.89, 1.39; P=0.36 with alpha of 0.05). The hazard ratio represents the instantaneous risk of resolution from moderately bad or worse cough in the prednisolone group compared to placebo; a hazard ratio greater than 1 demonstrates a beneficial effect of prednisolone. The Weibull AFT model time ratio was 0.91 (95% CI

0.76, 1.10) indicating that the time to resolution was reduced by 9% (0.45 days) with prednisolone compared to placebo (P=0.34); the lower limit of the 95% CI did not exclude the 20% *a priori* minimum clinically important difference. Further (secondary analysis) adjustment for factors demonstrating possible imbalance at baseline (age, gender, influenza vaccine in last 12 months) and smoking, had no effect on the models (Table 2).

Day 2 to 4 symptom severity

Mean symptom severity scores (and residuals) were normally distributed. The mean (SD) symptom severity scores were 1.99 (0.99) and 2.16 (1.09) for the prednisolone and placebo groups respectively. Adjusting for center and baseline illness severity, the mean symptom severity difference was 0.20 (95% CI -0.40, 0.00, P=0.05) between prednisolone and placebo (Table 2, *a priori* alpha 0.001). With a mean symptom severity score of 2.16 in the placebo group, a difference of 0.20 equates to a relative reduction of 9.3%. The lower limit of the 95% CI of this reduction was 18.5%, and excluded the 20% *a priori* minimum clinically important difference. Additional adjustment for factors demonstrating imbalance at baseline and smoking, marginally attenuated the difference in means and reduced the strength of evidence against the null hypothesis (Table 2).

Sensitivity analyses (see Online Supplement)

None of the sensitivity analyses had any effect on the primary comparisons: including those with no moderately bad or worse cough at baseline; multiple imputation of missing data; per protocol analysis; adjusting for day of recruitment (Web Table 1).

Secondary outcomes

There were no significant effects on any symptom duration or peak flow up to 28 days, or cough duration to 56 days (Table 3). Neither were any significant effects observed for: antibiotic use; patient satisfaction or intention to use the same treatment if it were to be available in the future; non-serious adverse events (Table 3), expected, unexpected or cough-related adverse events, or reconsultations (Web Table 2). The nature of the adverse events was similar between the groups (Web Table 3), no new urinary or visual symptoms were reported, and none of the patients reporting fatigue, thirst and dry throat (Web Table 3) had diabetes. There were no serious adverse events. Four participants (3 prednisolone and 1 placebo) attended accident and emergency but were not hospitalized.

Absolute measures of between-group differences

To aid interpretation, Table 4 presents absolute measures of effect for the primary outcome of duration of moderately bad or worse cough and the time-to-event secondary outcomes reported in Table 3. There is no single absolute measure of treatment effect for time-to-event data as it will vary over the duration of

follow-up; it can, however, be calculated at a specific time point. Of particular clinical interest is day 7, because this is a time in the illness trajectory when clinicians and patients want to know about expected benefits, and when steroids should have affected symptoms if effective. Survival curves were produced from the Cox regressions presented in Tables 2 and 3 at given values of center (Bristol) and duration of prior cough (median value). Predicted survival probabilities at day 7 in the prednisolone and placebo groups were obtained and an absolute risk difference estimated as the survival probability in the prednisolone group minus that in the placebo group. 95% confidence intervals were obtained using the method proposed by Altman and Andersen.[24] As an example of interpretation, for duration of moderately bad or worse cough the absolute difference in percentage unresolved at day 7 is -3.61 (95% CI -10.64, 4.23); this can be interpreted as 3.61% fewer prednisolone patients who still have an unresolved moderately bad or worse cough at the end of day 7. Absolute risk differences were also obtained (with 95% confidence intervals) for the binary secondary outcomes of antibiotic use (up to 7 and 28 days), patient satisfaction and intention to use the same treatment if it were to be available.

Subgroup analyses

All 95% confidence intervals for the interaction effects included values consistent with no significant subgroup effect (Web Table 4).

DISCUSSION

In this randomized trial of 401 adults, five days of moderate dose oral prednisolone did not reduce the duration of moderately bad or worse cough, or the severity of symptoms between days 2 and 4, in non-asthmatic adults who presented to primary care with ALRTI. Neither were any effects observed for the duration and severity of any ALRTI symptom, the duration of abnormal peak flow, antibiotic consumption or adverse events, including worsening of glycemic control in patients with diabetes.

The study has several strengths. It was an adequately powered, multicenter, fully masked, randomised trial, with low rates of missing baseline and follow up data. The design was pragmatic, using eligibility criteria easily reproduced in routine clinical practice and clinically relevant, validated[18] outcomes. The final sample included participants with high rates self-reported sputum production and wheeze, and was generalizable to non-asthmatic adults presenting to primary care with ALRTI in whom an immediate antibiotic is not necessary. With 398 participants, this trial more than doubles the number of patients recruited to primary care trials of corticosteroids for ALRTI,[15] and to our knowledge, is the first to investigate the effects of oral rather than inhaled steroids. The trial also contributes to a growing body of evidence suggesting systemic and topical corticosteroids have a limited role in the treatment of common infections and their post-infectious complications in primary care.[25,26] This contrasts with an increasing number of studies suggesting corticosteroids are effective for secondary care patients with community acquired pneumonia[27] croup,[28] acute sinusitis [29] and severe sore throat.[30]

This study also has several limitations. First, the low patient recruitment rate suggests patients may have been selectively invited to participate, affecting the generalizability of the final sample. However, the rate was faster than a similar previous trial,[19] not all practices were active throughout the recruitment period, and the characteristics of the final sample appears representative of primary care adult patients with ALRTI. Second, there were a higher than expected number of participants with zero duration of moderately bad or worse cough, though a sensitivity analysis including these participants did not influence the results. Third, other baseline biomarkers (e.g. inflammatory, microbiological, spirometric or radiographic) were not measured and it is possible that patients with more severe, inflammatory, eosinophilic[31,32] or microbiological (e.g. rhinovirus)[33] etiology entered the trial or could have differentially benefited. However, the study used readily recognized, pragmatic entry criteria facilitating replication in routine clinical practice. Fourth, study eligibility criteria might have included some patients with chronic or postinfectious cough, rather than ALRTI. However, 100% of participants had evidence of active lower respiratory tract involvement (sputum, shortness of breath, wheeze or chest pain) and over 75% had a pre-consultation cough duration <21 days. Fifth, the study used a patient-reported outcome rather than an objective primary outcome measure (such as digitally measured cough severity). This was chosen because it was considered the strongest option in the presence of a fully masked intervention; it closely reflected patient

priorities; and it allowed comparison with other trials.[4,19] Sixth, the lack of effects and a similar between-group pattern of adverse events could reflect poor adherence. However, this is unlikely as standard methods[34] were used to establish similar and high levels of adherence to both prednisolone and placebo, and adverse events were similar to another trial in which a similar dose of prednisolone was proven effective.[34]

The trial suggests oral corticosteroids should not be used in non-asthmatic/non-COPD adults in primary care who do not require treatment with an immediate antibiotic. Further research is needed to establish effectiveness in primary care patients with more severe infections, such as those with raised C-reactive protein, or requiring immediate antibiotic treatment, and larger studies or meta-analysis are needed to address effects in subgroups, such as those with longer pre-consultation illness and non-smokers.[15]

Conclusions

Among adults without asthma who developed ALRTI, the use of oral prednisolone for five days did not reduce symptom duration or severity. These findings do not support oral steroids for treatment of ALRTI in the absence of asthma.

AUTHOR CONTRIBUTIONS

Alastair Hay (ADH) was responsible for overall study design, management and data interpretation. ADH led the writing of, and approved, the final manuscript. Paul Little (PL), Michael Moore (MVM), Anthony Harnden (AH), Matthew Thompson (MT), Kay Wang (KW), Denise Kendrick (DK), Elizabeth Orton (EO), Sandra Hollinghurst (SPH) and Fran Carroll (FC) made substantial contributions to overall study design and to writing, and reviewed the final manuscript. Margaret May (MM) contributed to the design of statistical analyses and reviewed the final manuscript. Sara Brookes (STB) was lead study statistician and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. She led the data analyses, contributed to the writing and reviewed the final manuscript. Grace Young (GY) conducted the data analysis, writing and reviewed the final manuscript. Harriet Downing (HD) was the study manager, contributed to and reviewed the final manuscript. David Timmins (DT), Kate Martinson (KM) and Natasher Lafond (NL) were study co-ordinators, and contributed to and reviewed the final manuscript. ADH is guarantor for the study and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

CONFLICT OF INTEREST DISCLOSURES

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Thompson reported that he has received funding from Alere Inc to conduct research on C-reactive protein point-of-care tests, has received funding from Roche Molecular Diagnostics for consultancy work, and is a cofounder of Phoresa Inc, which is developing point-of-care tests for primary care.

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ROLE OF THE FUNDER/SPONSOR

The sponsor was the University of Bristol. Neither the funder nor the sponsor had no involvement in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

DISCLAIMER

The views expressed herein are those of the authors and not necessarily those of the NIHR, the National Health Service or the UK Department of Health.

NON-AUTHOR CONTRIBUTIONS

We thank the participants, the recruiting primary care sites, the National Institute for Health Research (NIHR) Clinical Research Network, and all members of the OSAC team. We would also like to thank the Trial Steering Committee (who provided independent supervision on behalf of the funder and sponsor) and Data Monitoring Committee (who oversaw safety) members, Nottingham University Hospitals NHS Trust pharmacy and the University Hospitals Bristol NHS Foundation Trust. We thank Professor Mark Ebell MD (University of Georgia) who (without compensation) conducted a secondary data analysis to estimate the use of oral prednisolone for ALRTI using administrative data from the southeastern US.

TABLES

Table 1. Baseline characteristics of randomized patients, by treatment group

	Prednisolone (N=198)	**Placebo** (N=200)
Center, n (%)		
Bristol	118 (60%)	113 (57%)
Oxford	39 (20%)	45 (23%)
Southampton	24 (12%)	21 (11%)
Nottingham	17 (9%)	21 (11%)
Demographics and past medical history		
Gender, n (%) male	82 (41%)	66 (33%)
Age in years, mean (SD)	50.0 (16.1)	44.8 (15.5)
Weight kg, median (IQR)[a]	77.0 (64.5,91.0)	76.0 (66.5,90.5)
Height cm, median (IQR)[b]	168.0 (161.0,175.0)	168.0 (163.0,176.0)
Ethnicity, n (%) white[c]	188 (95%)	193 (97%)
Occupation, n (%)		
Employed	137 (69%)	143 (72%)
Unemployed	17 (9%)	21 (11%)
Retired	41 (21%)	30 (15%)
Full-time education	3 (2%)	6 (3%)
Deprivation (IMD)[d], median (IQR)[e]	11.0 (5.0,23.0)	12.0 (5.0,23.0)
Smoking status, n (%)[f]		
Current	31 (16%)	38 (19%)
Past	63 (32%)	55 (28%)
Never	104 (53%)	106 (53%)
Lives with smoker, n (%)[g]	25 (14%)	32 (16%)
Received asthma medication >5 years previously[h]	10 (5%)	8 (4%)
Personal history of hay fever[i]	41 (22%)	46 (24%)
Personal history of eczema[j]	30 (16%)	26 (14%)
Family history asthma or hay fever or eczema, n (%)[k]	73 (40%)	76 (40%)
Influenza vaccine in last 12 months, n (%)	63 (32%)	44 (22%)
Recruited in winter (1st Oct-31st March)	112 (57%)	114 (57%)
Clinical characteristics and management		
Prior duration of cough (days), median (IQR)	13.0 (7.0,20.0)	10.0 (6.0,17.5)
Sputum (present within last 24 hours), n (%)[l]	149 (76%)	156 (78%)
Shortness of breath (present within last 24 hours) n (%)	146 (74%)	133 (67%)
Wheeze (present within last 24 hours), n (%)[l]	88 (45%)	98 (49%)
Chest pain (present within last 24 hours) n (%)	88 (44%)	97 (49%)
Patient reported illness severity at assessment (0-10), median (IQR)[m]	6.0 (5.0,7.0)	5.0 (4.0,7.0)
Pulse rate (bpm), mean (SD)	77.8 (12.3)	77.7 (11.8)
Temperature (^{o}C), mean (SD)	36.6 (0.5)	36.6 (0.4)
Oxygen saturation (%), mean (SD)[n]	97.5 (1.3)	97.8 (1.1)
Abnormal peak flow (less than 80% of expected peak	87 (44%)	79 (40%)

flow)[o]		
Respiratory rate (breaths per minute)[p]	15.4 (2.5)	15.0 (2.4)
Abnormal respiratory rate (more than 20 breaths per minute), n (%)	2 (1%)	1 (1%)
Chest retraction or prolonged expiration	0 (0%)	1 (1%)
Wheeze or rhonchi (auscultation), n (%)	11 (6%)	11 (6%)
Crackles or crepitations (auscultation), n (%)[q]	4 (2%)	6 (3%)
Bronchial breathing, n (%)	0 (0%)	2 (1%)
Taken prescribed β agonist in past 24 hours, n (%)	9 (5%)	3 (2%)
Over-the-counter drugs taken for current cough, n (%)	128 (65%)	139 (70%)
Given delayed antibiotic prescription, n (%)	22 (11%)	25 (13%)

[a] Weight missing for 2 prednisolone participants
[b] Height missing for 1 prednisolone participant
[c] Ethnicity missing for 1 placebo participant
[d] English Index of Multiple Deprivation scores (2015) [Geoconvert: UK Data Service Census Support], possible range 0-100; higher scores indicate higher levels of deprivation
[e] IMD missing for 2 prednisolone and 7 placebo participants
[f] Smoking status missing for 1 placebo participant
[g] Living with smoker missing for 15 prednisolone and 5 placebo participants
[h] Personal history of asthma missing for 10 prednisolone patients and 7 placebo patients
[i] Personal history of hayfever missing for 10 prednisolone patients and 11 placebo patients
[j] Personal history of eczema missing for 14 prednisolone patients and 10 placebo patients
[k] Family history of hay fever or eczema or asthma missing for 16 prednisolone and 11 placebo participants
[l] Sputum and wheeze presence in last 24 hours, missing for 1 prednisolone participant
[m] Patient reported illness severity 0 (completely well) to 10 (extremely unwell), missing for 1 prednisolone participant
[n] Oxygen saturation missing for 1 prednisolone participant
[o] Baseline abnormal peak flow was missing for 1 prednisolone patient
[p] Respiratory rate missing for 2 prednisolone and 1 placebo patient as only collected for those with a 'normal' rate
[q] Includes unilateral and bilateral

Table 2. Primary analyses

	Prednisolone		Placebo		Prednisolone vs. placebo			
	N	Median (95% CI)	N	Median (95% CI)	Hazard ratio (95% CI)	P value (alpha=0.05)	Time Ratio[a] (95% CI)	P value (alpha=0.05)
Duration (days) of moderately bad or worse cough (censored at 28 days)	173	5 (4,5)	161	5 (4,6)				
Adjusted for center and baseline[b]					1.11 (0.89, 1.39)	0.36	0.91 (0.76, 1.10)	0.34
Secondary additional adjustment[c,d]					1.09 (0.87, 1.37)	0.44	0.92 (0.76, 1.12)	0.40
	N	Mean (95% CI)	N	Mean (95% CI)	Difference in means (95% CI)			P value (alpha=0.001)
Mean symptom severity score (days 2-4)[e]	188	1.99 (1.85, 2.13)	181	2.16 (2.00, 2.32)				
Adjusted for center and baseline[b,f]					-0.20 (-0.40, 0.00)			0.054
Secondary additional adjustment[c,d,f]					-0.17 (-0.37, 0.04)			0.110

[a] Time ratio can be interpreted as the relative increase or decrease in time to resolution of moderately bad or worse cough in the prednisolone group compared to placebo group

[b] Baseline measure for duration of cough is prior duration of cough (1-28 days) and for mean symptom severity score is patient reported illness severity (0 – 10).

[c] Adjusted for center, baseline (as detailed in footnote b), factors showing baseline imbalance (age, gender, influenza vaccine) and smoking

[d] Smoking status missing for 1 placebo participant

[e] See *Methods, Primary Outcomes* for derivation of mean symptom severity score (minimum of 0 and maximum of 6 (most severe)).

[f] Patient reported illness severity missing for 1 prednisolone participant

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	Prednisolone (N=192)	**Placebo (N=182)**	**Prednisolone vs. placebo Adjusted for center and baseline[a]**	
	Mean area under curve[b,c] (95% CI)	Mean area under curve[b,c] (95% CI)	Difference in mean area under curve (95% CI)	P value
Cough	40.16 (36.67, 43.65)	42.88 (38.88, 46.87)	-2.43 (-7.66, 2.80)	0.36
Phlegm	25.48 (22.19, 28.78)	30.01 (26.40, 33.61)	-4.10 (-8.89, 0.70)	0.09
Shortness of breath	16.10 (13.25, 18.95)	18.39 (15.16, 21.61)	-2.30 (-6.34, 1.75)	0.27
Wheeze	12.32 (9.69, 14.96)	13.24 (10.37, 16.11)	0.18 (-3.27, 3.64)	0.92
Blocked or runny nose	19.83 (16.38, 23.28)	20.06 (17.12, 23.00)	0.67 (-3.70, 5.05)	0.76
Chest pain	6.64 (4.95, 8.33)	9.59 (6.98, 12.19)	-2.92 (-5.83, -0.01)	0.05
Fever	2.98 (2.05, 3.91)	3.45 (2.07, 4.82)	-0.33 (-1.90, 1.24)	0.68
Muscle ache	8.83 (6.71, 10.96)	10.29 (7.53, 13.06)	-1.61 (-4.99, 1.77)	0.35
Headache	10.77 (8.27, 13.28)	11.83 (8.89, 14.77)	-0.62 (-4.34, 3.09)	0.74
Sleep disturbance	20.80 (17.66, 23.94)	22.11 (18.13, 26.10)	-0.75 (-5.60, 4.10)	0.76
Feeling generally unwell	19.83 (17.22, 22.45)	22.68 (19.17, 26.19)	-3.25 (-7.38, 0.89)	0.12
Activity disturbance	14.29 (12.01, 16.57)	19.07 (15.40, 22.74)	-4.78 (-8.86, -0.69)	0.02
	Median (95% CI)[g]	Median (95% CI)[g]	Hazard ratio (95% CI)	P value
Duration (days) of moderately bad or worse cough (censored at 56 days)[d]	5 (4,5)	5 (4,6)	1.11 (0.89, 1.39)	0.36
Duration (days) of any cough (censored at 56 days)[e]	18 (17,23)	20 (17, 25)	1.13 (0.90, 1.42)	0.29
Duration (days) of abnormal peak flow (censored at 28 days)[f]	10 (7, 17)	11 (8,17)	1.10 (0.79, 1.52)	0.58

Table 3 continued

	Prednisolone (N=192)	**Placebo (N=182)**	**Prednisolone vs. placebo Adjusted for center and baseline[a]**	
	n, (% {95% CI})[i]	n, (% {95% CI})[i]	OR (95% CI)	P value
Consumption of antibiotics				
Up to 7 days	15, (8 {4, 12})	15, (8 {4, 12})	0.98 (0.42, 2.28)	0.96
Up to 28 days	28, (15 {10, 20})	34, (19 {13, 24})	0.78 (0.44, 1.39)	0.39
Patient satisfaction: Participant agrees trial tablets helped them feel better[h]	60, (34 {27, 41})	43, (25 {19, 32})	1.46 (0.92, 2.34)	0.11
Participant agrees they would take trial tablets in future[i]	99, (56 {48, 63})	81, (47 {40, 55})	1.36 (0.89, 2.08)	0.16
Any adverse events[j]				
0	151 (77 {71, 83})	162 (82 {76, 87})	1.26 (0.77, 2.07)[k]	0.36
1	36 (18 {13, 25})	24 (12 {8, 17})		
>1	9 (5 {2, 9})	12 (6 {3, 10})		

[a] Baseline measure for cough area under curve (AUC), duration of moderately bad or worse cough (56 days), any cough (56 days) and abnormal peak flow is prior duration of cough (days); for all symptoms (AUC) (with the exception of cough) baseline measure is presence or absence of symptom at baseline (previous 24 hours); and for antibiotic consumption, whether participant given delayed antibiotic prescription (Y/N). No baseline measures available for patient satisfaction, taking tablets in future or adverse events.

[b] For derivation of symptom area under curve see *Online supplement: Methods, Statistical analyses, Analysis of secondary outcomes*.[35]

[c] Missing data - AUC analysis includes: 185 prednisolone and 179 placebo participants for cough; 184 prednisolone and 179 placebo participants for phlegm, shortness of breath; 183 prednisolone and 179 placebo participants for wheeze, sleep disturbance; 182 prednisolone and 179 placebo participants for blocked or runny nose, chest pain, fever, muscle ache, headache, feeling generally unwell, activity disturbance.

[d] 5 patients in each group had unresolved moderately bad or worse cough at day 28. Total duration (up to 56 days) obtained for 3 prednisolone and 5 placebo patients.

[e] 61 prednisolone and 63 placebo patients had unresolved cough (score<1) at day 28. Total duration (up to 56 days) obtained for 38 prednisolone and 50 placebo patients.

[f] 18 prednisolone and 25 placebo patients had abnormal peak flow at 28 days. Post-hoc sensitivity analysis removed 6 prednisolone patients rated at baseline as poor at measuring peak flow – there was no impact on the model.

[g] Missing data - Duration of moderately bad or worse cough (56 days) analysis includes 173 prednisolone and 161 placebo participants (participants without moderately bad or worse cough on day 1 excluded); duration of any cough (56 days) analysis includes 191 prednisolone and 182 placebo participant; duration of abnormal peak flow analysis includes 117 prednisolone and 115 placebo participants (participants with normal peak flow on day 1 excluded).

[h] For derivation see *Online supplement: Methods, Statistical analyses, Analysis of secondary outcomes*

[i] Missing data - Antibiotic consumption analyses include 191 prednisolone and 182 placebo participants; patient satisfaction analyses include 178 prednisolone and 171 placebo.

[j] Excludes the duplicate participant who did experience an expected adverse event during their duplicate entry

[k] Ordinal logistic regression, adjusting for center and baseline patient reported illness severity, missing for 1 participant.

Table 4: Estimates of absolute between-group differences for time-to-event and binary outcomes

Time-to-event outcomes	Prednisolone			Placebo			Absolute difference in % unresolved[b] (95% CI) Adjusted for center and baseline[c]
		Unresolved at end of day 7			Unresolved at end of day 7		
	N[a]	n	% (95% CI)	N[a]	n	% (95% CI)	
Duration (days) of moderately bad or worse cough	173	51	30.64 (23.89, 37.63)	161	44	29.19 (22.33, 36.38)	-3.61(-10.64, 4.23)
Duration (days) of any cough	191	164	88.36 (82.86, 92.18)	182	154	88.91 (83.34, 92.70)	-1.28 (-4.07, 1.00)
Duration (days) of abnormal peak flow	117	62	59.26 (49.56, 67.71)	115	63	60.32 (50.67, 68.67)	-2.89 (-14.10, 6.83)
Binary outcomes	**N[a]**	**n**	**% (95% CI)**	**N[a]**	**n**	**% (95% CI)**	**Absolute difference in % (95% CI) Adjusted for center and baseline[d]**
Consumption of antibiotics	191			182			
Up to 7 days		15	7.85 (4.00, 11.70)		15	8.24 (4.21, 12.28)	-0.09 (-5.13, 4.94)
Up to 28 days		28	14.66 (9.60, 19.72)		34	18.68 (12.96 24.40)	-3.26 (-10.53, 4.02)
Patient satisfaction: Participant agrees trial tablets helped them feel better	178	60	33.71 (26.70, 40.72)	171	43	25.15 (18.88, 31.71)	7.74 (-1.85, 17.34)
Participant agrees they would take trial tablets in future	178	99	55.62 (48.25,62.99)	171	81	47.37 (39.81, 54.93)	7.48 (-3.02, 17.97)

[a] N refers to the number of participants with data available for the outcome of interest and included in the analysis.

[b] Absolute difference is calculated as the percentage unresolved at end of day 7 in prednisolone group minus the percentage in placebo group. A negative value for the absolute risk difference indicates that a smaller percentage of prednisolone patients will have unresolved cough or abnormal peak flow at end of day 7 than placebo patients.

[c] For time-to event outcomes adjusted analyses consider an 'average' value of covariates: Center = Bristol (where 60% of patients were recruited from) and prior duration of cough = 12 days (median value in sample).

[d] Baseline measure for consumption of antibiotics is whether participant was given delayed antibiotic prescription at baseline (Y/N). No baseline measures available for patient satisfaction or taking tablets in future.

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