Supplementary Online Content

Hayward GN, Hay AD, Moor AV, et al. Effect of oral dexamethasone without immediate antibiotics vs placebo on acute sore throat in adults: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2017.3417

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods: Protocol and statistical analysis plan amendments

Protocol Amendments

There have been 7 amendments to the protocol.
Amendment 1, 10-APR-2013, was to clarify some data points, ensuring that the CRFs and protocol were reflective of each other.
Amendment 2, 08-JUL-2013, amended the sample size and added to the follow up process the addition of a £10 thank you for those who return their completed Symptom Diary to the PC-CTU and also added in additional reminder text messages to remind participants to complete and return the Symptom Diary.
Amendment 3, 02-SEP-2013, added Johanna Maughan and Julie Allen as investigators on the trial.
Amendment 4, 14-FEB-2014, added an upper age limit of 70 years to the inclusion/exclusion criteria.
Amendment 5, 02-JUN-2014, listed additional research sites.
Amendment 6, 23-JUL-2014 increased the value of the gift card sent to participants to £20 and clarified the wording of SAE reporting within the protocol.
Amendment 7, 16-FEB-2015, listed an additional research site.

The following two outcomes in our initial protocol were not analysed: difficulty swallowing and pain on swallowing over the 7 days from treatment onset, severity of symptoms in the 2-4 days after randomisation. These outcomes were removed as they were duplicated in the duration of moderately bad symptoms diary analysis. Cost effectiveness analysis will be reported in a separate publication

We confirm that the outcomes in our published protocol were the outcomes pre-specified before the trials commenced and there have been no changes to the primary outcome since inception of the trial.

Deviations from Statistical Analysis Plan:

The total number of days reporting at least moderately bad symptoms were analysed using a negative binomial model adjusting for centre, delayed prescriptions at baseline and including the number of completed diary days as an offset. This is a deviation from the Statistical Analysis Plan, which states that a random effects negative binomial model would be used for this analysis. None of the incidence rate ratios for the multiple symptoms show that there is a difference in the number of days reporting moderately bad symptoms or worse over 7 days by treatment group.
A sensitivity analysis for time to onset of pain relief and complete symptom relief within 7 days was carried out as an ad hoc additional sensitivity analysis. Where time to pain relief and time to symptom relief were incomplete but an event had occurred, the time of relief was estimated as the same time of the day as when the medication was taken (for example, if symptom relief occurred on day 3 with no time specified, the time was replaced with (24 hours X 3 days) from the time of medication). Participants who had no event (censored) but no last recorded time of contact were replaced as censored exactly (7 days X 24 hours) from when the medication was taken. Participants who did not fully complete the 7 day diary and have reported no symptom relief at day 7 will be assumed to have no pain relief and censored at day 7.
Subgroup analysis was carried out on the primary and primary secondary outcomes of complete sore throat resolution at 24 hours and 48 hours by whether a streptococcal organism was detected at baseline.

The duration of taking over the counter medications was conducted as an ad hoc analysis. The frequency of daily antibiotic use for participants that were not prescribed delayed antibiotics were reported as a post hoc analysis. Following an alternative definition for sore throat complications to include sinusitis, otitis media and cellulitis, a post-hoc analysis was conducted to re-explore the re-presentation to the GP/OOH A&E.

eTable 1 Baseline clinician rated symptoms[a]

Baseline Symptoms	*Full Cohort*		*No Antibiotics*		*Delayed Antibiotics*	
	Dexameth[b] (N= 288)	*Placebo (N=277)*	*Dexameth (N= 288)*	*Placebo (N=277)*	*Dexameth (N= 288)*	*Placebo (N=277)*
Sore Throat						
None	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Slight	11 (3.8%)	9 (3.3%)	8 (4.6%)	5 (3.0%)	3 (2.6%)	4 (3.7%)
Moderate	185 (64.2%)	177 (63.9%)	110 (63.6%)	108 (63.9%)	75 (65.2%)	69 (63.9%)
Severe	92 (31.9%)	91 (32.9%)	55 (31.8%)	56 (33.1%)	37 (32.2%)	35 (32.4%)
Runny Nose in Last 24 Hours						
None	162 (56.3%)	139 (50.2%)	96 (55.5%)	80 (47.3%)	66 (57.4%)	59 (54.6%)
Slight	73 (25.4%)	79 (28.5%)	43 (24.9%)	47 (27.8%)	30 (26.1%)	32 (29.6%)
Moderate	47 (16.3%)	53 (19.1%)	30 (17.3%)	37 (21.9%)	17 (14.8%)	16 (14.8%)
Severe	6 (2.1%)	6 (2.2%)	4 (2.3%)	5 (3.0%)	2 (1.7%)	1 (0.9%)
Runny Nose During Illness						
None	160 (55.6%)	146 (52.7%)	95 (54.9%)	82 (48.5%)	65 (56.5%)	64 (59.3%)
Slight	79 (27.4%)	83 (30.0%)	48 (27.8%)	52 (30.8%)	31 (27.0%)	31 (28.7%)
Moderate	44 (15.3%)	41 (14.8%)	26 (15.0%)	29 (17.2%)	18 (15.7%)	12 (11.1%)
Severe	5 (1.7%)	7 (2.5%)	4 (2.3%)	6 (3.6%)	1 (0.9%)	1 (0.9%)
Cough in Last 24 Hours						
None	130 (45.1%)	112 (40.4%)	72 (41.6%)	60 (35.5%)	58 (50.4%)	52 (48.2%)
Slight	83 (28.8%)	88 (31.8%)	54 (31.2%)	56 (33.1%)	29 (25.2%)	32 (29.6%)
Moderate	59 (20.5%)	64 (23.1%)	34 (19.7%)	45 (26.6%)	25 (21.7%)	19 (17.6%)
Severe	16 (5.6%)	13 (4.7%)	13 (7.5%)	8 (4.7%)	3 (2.6%)	5 (4.6%)
Cough During Illness						
None	127 (44.1%)	109 (39.4%)	68 (39.3%)	59 (34.9%)	59 (51.3%)	50 (46.3%)
Slight	87 (30.2%)	88 (31.8%)	57 (33.0%)	57 (33.7%)	30 (26.1%)	31 (28.7%)
Moderate	62 (21.5%)	68 (24.6%)	39 (22.5%)	46 (27.2%)	23 (20.0%)	22 (20.4%)
Severe	12 (4.2%)	12 (4.3%)	9 (5.2%)	7 (4.1%)	3 (2.6%)	5 (4.6%)
Hoarse Voice in Last 24 Hours						
None	113 (39.2%)	95 (34.3%)	67 (38.7%)	54 (32.0%)	46 (40.0%)	41 (38.0%)
Slight	92 (31.9%)	97 (35.0%)	48 (27.8%)	62 (36.7%)	44 (38.3%)	35 (32.4%)
Moderate	56 (19.4%)	59 (21.3%)	39 (22.5%)	35 (20.7%)	17 (14.8%)	24 (22.2%)
Severe	27 (9.4%)	26 (9.4%)	19 (11.0%)	18 (10.7%)	8 (7.0%)	8 (7.4%)
Hoarse Voice During Illness						
None	111 (38.5%)	86 (31.1%)	65 (37.6%)	52 (30.8%)	46 (40.0%)	34 (31.5%)
Slight	98 (34.0%)	108 (39.0%)	56 (32.4%)	66 (39.1%)	42 (36.5%)	42 (38.9%)
Moderate	60 (20.8%)	65 (23.5%)	40 (23.1%)	38 (22.5%)	20 (17.4%)	27 (25.0%)
Severe	19 (6.6%)	18 (6.5%)	12 (6.9%)	13 (7.7%)	7 (6.1%)	5 (4.6%)

eTable 1 Baseline clinician rated symptoms continued

Baseline Symptoms	*Full Cohort*		*No Antibiotics*		*Delayed Antibiotics*	
	Dexameth (N= 288)	***Placebo (N=277)***	***Dexameth (N= 288)***	***Placebo (N=277)***	***Dexameth (N= 288)***	***Placebo (N=277)***
Disturbed Sleep						
None	64 (22.2%)	59 (21.3%)	45 (26.0%)	36 (21.3%)	19 (16.5%)	23 (21.3%)
Slight	70 (24.3%)	67 (24.2%)	43 (24.9%)	41 (24.3%)	27 (23.5%)	26 (24.1%)
Moderate	91 (31.6%)	95 (34.3%)	49 (28.3%)	57 (33.7%)	42 (36.5%)	38 (35.2%)
Severe	63 (21.9%)	56 (20.2%)	36 (20.8%)	35 (20.7%)	27 (23.5%)	21 (19.4%)
Difficulty Swallowing						
None	17 (5.9%)	14 (5.1%)	12 (6.9%)	11 (6.5%)	5 (4.4%)	3 (2.8%)
Slight	73 (25.4%)	67 (24.2%)	47 (27.2%)	45 (26.6%)	26 (22.6%)	22 (20.4%)
Moderate	131 (45.5%)	137 (49.5%)	80 (46.2%)	75 (44.4%)	51 (44.4%)	62 (57.4%)
Severe	67 (23.3%)	59 (21.3%)	34 (19.7%)	38 (22.5%)	33 (28.7%)	21 (19.4%)
Generally Unwell						
None	45 (15.6%)	43 (15.5%)	32 (18.5%)	24 (14.2%)	13 (11.3%)	19 (18.6%)
Slight	94 (32.6%)	71 (25.6%)	55 (31.8%)	43 (25.4%)	39 (33.9%)	28 (25.9%)
Moderate	129 (44.8%)	138 (49.8%)	77 (44.5%)	89 (52.7%)	52 (45.2%)	49 (45.4%)
Severe	20 (6.9%)	25 (9.0%)	9 (5.2%)	13 (7.7%)	11 (9.6%)	12 (11.1%)
Fever in Last 24 Hours						
None	128 (44.4%)	135 (48.7%)	83 (48.0%)	86 (50.9%)	45 (39.1%)	49 (45.4%)
Slight	81 (28.1%)	71 (25.6%)	49 (28.3%)	43 (25.4%)	32 (27.8%)	28 (25.9%)
Moderate	70 (24.3%)	57 (20.6%)	38 (22.0%)	32 (18.9%)	32 (27.8%)	25 (23.2%)
Severe	9 (3.1%)	14 (5.1%)	3 (1.7%)	8 (4.7%)	6 (5.2%)	6 (5.6%)
Fever During Illness						
None	124 (43.1%)	128 (46.2%)	83 (48.0%)	86 (50.9%)	41 (35.7%)	42 (38.9%)
Slight	80 (27.8%)	70 (25.3%)	49 (28.3%)	40 (23.7%)	31 (27.0%)	30 (27.8%)
Moderate	74 (25.7%)	65 (23.5%)	38 (22.0%)	38 (22.5%)	36 (31.3%)	27 (25.0%)
Severe	10 (3.5%)	14 (5.1%)	3 (1.7%)	5 (3.0%)	7 (6.1%)	9 (8.3%)
Headache						
None	133 (46.2%)	111 (40.1%)	84 (48.6%)	64 (37.9%)	49 (42.6%)	47 (43.5%)
Slight	74 (25.7%)	73 (26.4%)	42 (24.3%)	45 (26.6%)	32 (27.8%)	28 (25.9%)
Moderate	65 (22.6%)	72 (26.0%)	40 (23.1%)	45 (26.6%)	25 (21.7%)	27 (25.0%)
Severe	16 (5.6%)	21 (7.6%)	7 (4.1%)	15 (8.9%)	9 (7.8%)	6 (5.6%)
Muscle Aches						
None	146 (50.7%)	129 (46.6%)	91 (52.6%)	82 (48.5%)	55 (47.8%)	47 (43.5%)
Slight	66 (22.9%)	67 (24.2%)	41 (23.7%)	45 (26.6%)	25 (21.7%)	22 (20.4%)
Moderate	57 (19.8%)	63 (22.7%)	30 (17.3%)	36 (21.3%)	27 (23.5%)	27 (25.0%)
Severe	19 (6.6%)	18 (6.5%)	11 (6.4%)	6 (3.6%)	8 (7.0%)	12 (11.1%)

eTable 1 Baseline clinician rated symptoms continued

Baseline Symptoms Continued	*Full Cohort*		*No Antibiotics*		*Delayed Antibiotics*	
	Dexameth (N= 288)	***Placebo (N=277)***	***Dexameth (N= 288)***	***Placebo (N=277)***	***Dexameth (N= 288)***	***Placebo (N=277)***
Abdominal Pain						
None	250 (86.8%)	240 (86.6%)	150 (86.7%)	146 (86.4%)	100 (87.0%)	94 (87.0%)
Slight	27 (9.4%)	24 (8.7%)	17 (9.8%)	16 (9.5%)	10 (8.7%)	8 (7.4%)
Moderate	10 (3.5%)	9 (3.3%)	5 (2.9%)	3 (1.8%)	5 (4.4%)	6 (5.6%)
Severe	1 (0.4%)	4 (3.3%)	1 (0.6%)	4 (2.4%)	0 (0%)	0 (0%)
Diarrhoea						
None	266 (92.4%)	256 (92.4%)	158 (91.3%)	157 (92.9%)	108 (93.9%)	99 (91.7%)
Slight	18 (6.3%)	14 (5.1%)	12 (6.9%)	9 (5.3%)	6 (5.2%)	5 (4.6%)
Moderate	4 (1.4%)	4 (1.4%)	3 (1.7%)	1 (0.6%)	1 (0.9%)	3 (2.8%)
Severe	0 (0%)	3 (1.1%)	0 (0%)	2 (1.2%)	0 (0%)	1 (0.9%)
Vomiting						
None	275 (95.5%)	262 (94.6%)	162 (93.6%)	163 (96.5%)	113 (98.3%)	99 (91.7%)
Slight	7 (2.4%)	10 (3.6%)	6 (3.5%)	3 (1.8%)	1 (0.9%)	7 (6.5%)
Moderate	6 (2.1%)	4 (1.4%)	5 (2.9%)	3 (1.8%)	1 (0.9%)	1 (0.9%)
Severe	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Earache						
None	159 (55.2%)	171 (61.7%)	92 (53.2%)	103 (61.0%)	67 (58.3%)	68 (63.0%)
Slight	81 (28.1%)	60 (21.7%)	52 (30.1%)	41 (24.3%)	29 (25.2%)	19 (17.6%)
Moderate	40 (13.9%)	36 (13.0%)	25 (14.5%)	20 (11.8%)	15 (13.0%)	16 (14.8%)
Severe	8 (2.8%)	10 (3.6%)	4 (2.3%)	5 (3.0%)	4 (3.5%)	5 (4.6%)

[a]Patient's symptoms were rated by the clinician as none, slight, moderate or severe according to clinical judgement. Data are frequency (%)

[b]Dexameth = Dexamethasone

eTable2 Sensitivity Analysis for Complete Sore Throat Resolution at 24 and 48 hours: missing responses assumed to be completely resolved[a]

Outcome	*Cohort*	*Complete resolution n/N (%)*		*Relative risk*	*95% Confidence interval*	*P-value*
		Dexamethasone	*Placebo*			
Complete resolution of sore throat at 24 hours	Full	86 (29.9%)	64 (23.1%)	1.3	0.98, 1.71	0.07
	No delayed antibiotic prescription	57 (33%)	43 (25.4%)	1.29	0.93, 1.81	0.13
	Delayed antibiotic prescription	29 (25.2%)	21 (19.4%)	1.3	0.79, 2.13	0.31
Complete resolution of sore throat at 48 hours	Full	121 (42%)	90 (32.5%)	1.29	1.04, 1.61	0.02
	No delayed antibiotic prescription	76 (43.9%)	56 (33.1%)	1.32	1.01, 1.73	0.045
	Delayed antibiotic prescription	45 (39.1%)	34 (31.5)	1.23	0.86, 1.75	0.27

[a]Relative risk of resolution of sore throat (benefit). Numbers greater than 1.0 represent increased probability of resolution of sore throat in treatment group. Participants with missing values assumed to have complete resolution of sore throat. Model adjusted for centre and whether given a delayed antibiotic prescription for full cohort

eTable3 Sensitivity Analysis for Complete Sore Throat Resolution at 24 and 48 hours: multiple imputation of missing data[a]

Outcome	*Cohort*	*Relative risk*	*95% Confidence interval*	*P-value*
Complete resolution of sore throat at 24 hours	Full	1.3	0.94, 1.81	0.12
	No delayed antibiotic prescription	1.34	0.88, 2.03	0.17
	Delayed antibiotic prescription	1.2	0.68, 2.11	0.54
Complete resolution of sore throat at 48 hours	Full	1.32	1.04, 1.69	0.03
	No delayed antibiotic prescription	1.39	1.02, 1.89	0.04
	Delayed antibiotic prescription	1.25	0.83, 1.87	0.29

[a]Multiple imputation (M=20) model contains variables included in the original model (treatment, centre and whether they had a delayed antibiotic prescription for the full cohort) and age at randomisation as this was identified as being predictive of non-response

eTable 4 Sensitivity Analysis for Complete Sore Throat Resolution at 24 and 48 hours: complete Case Analysis[a]

Outcome	*Cohort*	*Complete resolution n/N (%)*		*Relative risk*	*95% Confidence interval*	*P-value*
		Dexamethasone	*Placebo*			
Complete resolution of sore throat at 24 hours	Full	65/267 (24.3%)	49/262 (18.7%)	1.31	0.94, 1.82	0.11
	No delayed antibiotic prescription	43/159 (27%)	32/158 (20.3%)	1.33	0.89, 1.99	0.17
	Delayed antibiotic prescription	22/108 (20.4%)	17/104 (16.4%)	1.23	0.70, 2.18	0.47
Complete resolution of sore throat at 48 hours	Full	102/269 (37.9%)	75/262 (28.6%)	1.33	1.04, 1.69	0.02
	No delayed antibiotic prescription	65/162 (40.1%)	46/159 (28.9%)	1.38	1.01, 1.87	0.04
	Delayed antibiotic prescription	37/107 (34.6%)	29/103 (28.2%)	1.22	0.81, 1.82	0.34

[a]Relative risk of resolution of sore throat (benefit). Numbers greater than 1.0 represent increased probability of resolution of sore throat in treatment group. Participants with missing values not included in analysis. Model adjusted for centre and whether given a delayed antibiotic prescription for full cohort

eTable 5 Duration of moderately bad symptoms recorded by validated symptom diary over the 7 days from treatment onset present for all participants who returned a complete symptom diary[a]

Participants with complete symptom diary (N= 391)	*Dexamethasone N=194*		*Placebo N=197*			
	Median days [IQR]	**Mean days (SD)**	**Median days [IQR]**	**Mean days (SD)**	**IRR 95%CI***	**p value**
Sore throat	**1 [0,3]**	**1.9 (1.9)**	**1 [0,3]**	**1.9 (1.9)**	**1.1 (0.9, 1.3)**	**0.563**
No delayed prescription	1 [0,3]	1.9 (2.0)	1 [0,3]	1.8 (1.9)		
Delayed prescription	2 [1,3]	2.0 (1.7)	2 [1,3]	2.0 (1.9)		
Pain on swallowing	**1 [0,3]**	**1.6 (1.7)**	**1 [0,2]**	**1.5 (1.7)**	**1.1 (0.8, 1.4)**	**0.569**
No delayed prescription	1 [0,2]	1.4 (1.7)	1 [0,2]	1.4 (1.7)		
Delayed prescription	2 [0,3]	1.9 (1.7)	1 [0,3]	1.7 (1.9)		
Difficulty swallowing	**0 [0,2]**	**1.2 (1.6)**	**1 [0,2]**	**1.2 (1.7)**	**1.0 (0.7, 1.4)**	**0.947**
No delayed prescription	0 [0,2]	1.0 (1.5)	0 [0,1]	1.0 (1.5)		
Delayed prescription	1 [0,2]	1.4 (1.6)	1 [0,3]	1.5 (1.8)		
Feeling unwell	**1 [0,3]**	**1.7 (2.0)**	**1 [0,2]**	**1.6 (1.9)**	**1.1 (0.8, 1.4)**	**0.672**
No delayed prescription	1 [0,3]	1.6 (2.1)	1 [0,2]	1.4 (2.0)		
Delayed prescription	1 [0,3]	1.8 (2.0)	1 [0,3]	1.9 (1.9)		
Cough	**0 [0,3]**	**1.7 (2.5)**	**0 [0,2]**	**1.4 (2.2)**	**1.2 (0.8, 1.8)**	**0.329**
No delayed prescription	0 [0,3.5]	1.8 (2.5)	0 [0,2]	1.4 (2.2)		
Delayed prescription	0 [0,3]	1.6 (2.4)	0 [0,2]	1.3 (2.1)		
Fever	**0 [0,0]**	**0.4 (0.9)**	**0 [0,0]**	**0.5 (1.0)**	**0.7 (0.4, 1.2)**	**0.173**
No delayed prescription	0 [0,0]	0.3 (1.0)	0 [0,0]	0.4 (0.9)		
Delayed prescription	0 [0,0]	0.4 (0.9)	0 [0,1]	0.6 (1.2)		
Sleep disturbance	**0 [0,2]**	**1.4 (2.0)**	**1 [0,2]**	**1.4 (1.9)**	**1.1 (0.8, 1.5)**	**0.595**
No delayed prescription	0 [0,2]	1.4 (2.0)	0 [0,2]	1.3 (2.0)		
Delayed prescription	1 [0,2]	1.5 (3.7)	1 [0,2]	1.5 (3.4)		

eTable 5 Duration of moderately bad symptoms recorded by validated symptom diary over the 7 days from treatment onset present for all participants who returned a complete symptom diary continued

	Dexamethasone N=194	*Placebo N=197*

	Median days [IQR]	Mean days (SD)	Median days [IQR]	Mean days (SD)	IRR 95%CI*	p value
Tender glands in neck	**0 [0,2]**	**1.0 (1.6)**	**0 [0,2]**	**1.0 (1.6)**	**1.0 (0.7, 1.4)**	**0.890**
No delayed prescription	0 [0,1]	0.9 (1.5)	0 [0,1]	0.9 (1.6)		
Delayed prescription	0 [0,2]	1.2 (1.7)	1 [0,2]	1.3 (1.5)		
Change in mood	**0 [0,0]**	**0.6 (1.5)**	**0 [0,1]**	**0.6 (1.3)**	**1.3 (0.7, 2.2)**	**0.370**
No delayed prescription	0 [0,0]	0.5 (1.3)	0 [0,0]	1.6 (2.4)		
Delayed prescription	0 [0,1]	0.7 (1.3)	0 [0,2]	0.7 (1.4)		
Vomiting	**0 [0,0]**	**0.1 (0.7)**	**0 [0,0]**	**0.1 (0.4)**	**1.2 (0.3, 4.5)**	**0.815**
No delayed prescription	0 [0,0]	0.1 (0.9)	0 [0,0]	0.1 (0.4)		
Delayed prescription	0 [0,0]	0.1 (0.3)	0 [0,0]	0.1 (0.3)		

[a]Negative binomial model for the number of days of moderately bad symptoms adjusted for centre, delayed prescription and number of completed diary days as an offset

eTable 6: Change in ratings of sore throat pain, difficulty swallowing and pain on swallowing by visual analogue scale[a].

		Dexamethasone Mean (95%CI)	Placebo Mean (95%CI)	Mean difference (95%CI)	P-value
Sore throat pain					
Full	AUC Mean*	181.8 (173.5, 190.0)	179.7 (171.9, 187.5)	2.048 (-9.3, 13.4)	0.72
	Baseline, mean (SD)	61.1 (22.7)	62.5 (21.4)		
	Change from baseline to day 1**	-19.2 (-22.4, -16.0)	-15.9 (-19.2, -12.7)	-3.6 (-7.9, 0.6)	0.09
	Change from baseline to day 2**	-28.9 (-32.8, -25.0)	-30.3 (-34.5, -26.2)	0.5 (-4.7, 5.7)	0.85
No antibiotic	AUC Mean*	174.3 (163.4, 185.1)	174.6 (163.7, 185.5)	-0.336 (-15.6, 14.9)	0.97
	Baseline, mean (SD)	58.2 (22.7)	62.1 (21.9)		
	Change from baseline to day 1**	-19.5 (-23.3, -15.8)	-17.3 (-21.3,-13.2)	-3.3 (-8.6, 1.9)	0.21
	Change from baseline to day 2**	-29.2 (-33.7, -24.7)	-31.4 (-36.4,-26.5)	0.4 (-5.8, 6.6)	0.90
Delayed antibiotic	AUC Mean*	194.3 (181.9, 206.8)	187.7 (176.5, 198.9)	6.6 (-10.0, 23.3)	0.43
	Baseline, mean (SD)	65.8 (22.1)	63.1 (20.5)		
	Change from baseline to day 1**	-18.6 (-24.4, -12.9)	-13.7 (-19.1,-8.2)	-3.9 (-11.3, 3.5)	0.30
	Change from baseline to day 2**	-28.4 (-35.6, -21.1)	-28.4 (-35.9,-20.9)	1.2 (-8.3, 10.7)	0.80

eTable 6: Change in ratings of sore throat pain, difficulty swallowing and pain on swallowing by visual analogue scale continued

Continued		Dexamethasone Mean (95%CI)	Placebo Mean (95%CI)	Mean difference (95%CI)	P-value
Pain on swallowing					
Full	AUC Mean[b]	163.3 (153.6, 173.0)	165.0 (155.9, 174.1)	-1.7 (-15.0, 11.5)	0.80
	Baseline, mean (SD)	60.1 (25.8)	61.5 (24.1)		
	Change from baseline to day 1[c]	-21.6 (- 24.8,-18.3)	-18.2 (-21.6, -14.7)	-3.7 (-8.2, 0.8)	0.11
	Change from baseline to day 2[c]	-29.3 (-33.3, -25.3)	-32.9 (-37.2, -28.7)	2.9 (-2.3, 8.2)	0.27
No antibiotic	AUC Mean	149.7 (137.4, 162.0)	156.4 (143.9, 168.8)	-6.6 (-24.1, 10.8)	0.45
	Baseline, mean (SD)	55.1 (25.9)	59.7 (25.6)		
	Change from baseline to day 1	-21.4 (-25.3, -17.5)	-19.7 (-24.0, -15.4)	-3.0 (-8.5, 2.5)	0.28
	Change from baseline to day 2	-28.9 (-33.6, -24.3)	-33.9 (-39.1, -28.8)	2.9 (-3.2, 9.1)	0.35
Delayed antibiotic	AUC Mean	185.7 (171.0, 200.4)	178.2 (165.2, 191.2)	7.5 (-12.0, 26.9)	0.45
	Baseline, mean (SD)	68.2 (23.7)	64.4 (21.2)		
	Change from baseline to day 1	-21.8 (-27.7, -16.0)	-15.6 (-21.3,-9.9)	-5.2 (-13.1, 2.7)	0.20
	Change from baseline to day 2	-29.9 (-37.3, -22.5)	-31.3 (-38.8, -23.7)	3.0 (-6.8, 12.8)	0.54

eTable 6: Change in ratings of sore throat pain, difficulty swallowing and pain on swallowing by visual analogue scale continued

Continued		Dexamethasone Mean (95%CI)	Placebo Mean (95%CI)	Mean difference (95%CI)	P-value
Difficulty swallowing					
Full	AUC Mean	134.6 (124.0, 145.2)	143.5 (133.2, 153.8)	-8.9 (-23.6, 5.8)	0.24
	Baseline, mean (SD)	51.1 (30.4)	53.0 (29.2)		
	Change from baseline to day 1	-18.7 (-22.1, -15.2)	-15.5 (-19.1, -11.9)	-3.9 (-8.5, 0.6)	0.09
	Change from baseline to day 2	-26.7 (-30.9,-22.5)	-27.7 (-32.0, -23.3)	-0.0 (-5.1, 5.1)	0.99
No antibiotic	AUC Mean	123.5 (110.5, 136.5)	130.8 (117.0, 144.7)	-7.4 (-26.2, 11.5)	0.44
	Baseline, mean (SD)	46.0 (29.7)	49.7 (31.1)		
	Change from baseline to day 1	-18.6 (-22.5, -14.7)	-16.7 (-21.5, -11.9)	-3.4 (-8.9, 2.1)	0.22
	Change from baseline to day 2	-25.5 (-30.1, -20.9)	-27.5 (-32.9, -22.1)	0.37 (-5.4, 6.1)	0.90
Delayed antibiotic	AUC Mean	153.4 (135.7, 171.1)	163.0 (148.1, 177.9)	-9.6 (-32.6, 13.4)	0.41
	Baseline, mean (SD)	59.6 (29.7)	58.4 (25.0)		
	Change from baseline to day 1	-18.8 (-25.5, -12.1)	-13.6 (-19.2, -8.0)	-5.0 (-13.1, 3.1)	0.23
	Change from baseline to day 2	-28.7 (-36.9, -20.5)	-27.9 (-35.3, -20.6)	-0.6 (-10.5, 9.2)	0.90

[a]Visual analogue scales were 100mm in length, with possible scores in mm from 0 to 100. A score of 0 was indicative of No pain or difficulty, 100 indicated the worst pain or difficulty imaginable.

[b]AUC calculated using trapezoidal rule with estimates from mixed effects repeated measures model adjusting for symptom at baseline, centre, and delayed antibiotic prescription.

[c]Linear regression model adjusting for symptom at baseline, centre and delayed antibiotic prescription

Number of respondents (D = dexamethasone P = Placebo). Full cohort: Means D=193 P=194; Day 1 D=191 P=193; Day 2 D 188 P 191; No antibiotics: Means D=120 P=120; Day 1 D=120 P=118; Day 2 D=117 P=119. Delayed antibiotics: Means D=73 P=73; Day 1 D=72 P=73; Day 2 D=72 P=71.

eTable 7 Sensitivity analysis for Time to Onset of Pain relief and Time to Complete Resolution of pain

	Dexamethasone Median (25^{th} – 75^{th} centile)	N	Placebo Median (25^{th} – 75^{th} centile)	N	Hazard ratio (95%CI)	p value
Time to onset of pain relief in hours*						
Full cohort	27.9 (22.7 to 52.8)	191	26.3 (23.6 to 56.4)	192	1.066(0.868, 1.309)	0.54
No antibiotics	27.5 (21.5 to 48)	117	24.5 (23.4 to 48)	121	1.017 (0.782, 1.322)	0.90
Delayed antibiotics	28.5 (23.2 to 60.0)	74	34.7 (24 to 69.3)	71	1.144 (0.815, 1.605)	0.44
Time to complete symptom resolution in hours^						
Full cohort	92.5 (46.0 to 165.1)	194	94.0 (48.0 to 168.0)	194	1.019 (0.809, 1.284)	0.87
No antibiotics	92.1 (45.7, 168.0)	120	93.5 (48.0 to 168.0)	122	1.001 (0.745, 1.347)	0.99
Delayed antibiotics	96.0 (46.0 to 163.5)	74	94.7 (48.0 to 165.1)	72	1.033 (0.712, 1.499)	0.86

*2 participants (1 from each treatment group) were excluded from the time-to-onset analysis for having values outside the feasible range i.e., <0 or >200 hours. Participants who did complete any days of their symptom diary were excluded from the analysis (n=174/565) and all with “NA” in answer to "Has your sore throat become less painful in the last 24 hours?" are assumed to have missing data and excluded from the analysis (n=6/565). All without a recorded hour and minute of pain relief onset (reported by the participant) were assumed to experience pain relief at the same point in the day as their baseline diary time (including those censored and lost to follow up). The event time for censored participants was the day and time of diary completion or the instance of lost to follow up, if provided. Cox Regression model adjusted for delayed antibiotic prescription at baseline and centre

^3 participants (all from the placebo arm) were excluded from the time-to-resolution analysis for having time-to-event values outside the feasible range i.e., <0 or >200 hours. Participants who did not complete any days of their symptom diary were excluded from the analysis (n=174/565). All without a recorded hour and minute of symptom resolution onset (reported by the participant) were assumed to experience symptom resolution at the same point in the day as their baseline diary time (including those censored and lost to follow up). The event time for censored participants was the day and time of diary completion or the instance of lost to follow up, if provided. Cox Regression model adjusted for delayed antibiotic prescription at baseline and centre