

A Longitudinal Assessment of Acute Cough

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Rationale: Cough can be assessed with visual analog scales (VAS), health status measures, and 24-hour cough frequency monitors (CF₂₄). Evidence for their measurement properties in acute cough caused by upper respiratory tract infection (URTI) and longitudinal data is limited.

Objectives: To assess cough longitudinally in URTI with subjective and objective outcome measures and determine sample size for future studies.

Methods: Thirty-three previously healthy subjects with URTI completed cough VAS, Leicester Cough Questionnaire (LCQ-acute), and CF₂₄ monitoring (Leicester Cough Monitor) on three occasions, 4 days apart. Changes in subjects' condition were assessed with a global rating of change questionnaire. The potential for baseline first-hour cough frequency (CF₁), VAS, and LCQ to identify low CF₂₄ was assessed. **Measurements and Main Results:** Mean $\pm$ SD duration of cough at visit 1 was 4.1 ± 2.5 days. Geometric mean $\pm$ log SD baseline CF₂₄ and median (interquartile range) cough bouts were high (14.9 ± 0.4 coughs/h and 85 [39–195] bouts/24 h). Health status was severely impaired. There was a significant reduction in CF₂₄ and VAS, and improvement in LCQ, from visits 1–3. At visit 3, CF₂₄ remained above normal limits in 52% of subjects. The smallest changes in CF₂₄, LCQ, and VAS that subjects perceived important were 54%, 2- and 17-mm change from baseline, respectively. The sample sizes required for parallel group studies to detect these changes are 27, 51, and 25 subjects per group, respectively. CF₁ (<20.5 coughs/h) was predictive of low CF₂₄.

Conclusions: CF₂₄, VAS, and LCQ are responsive outcome tools for the assessment of acute cough. The smallest change in cough frequency perceived important by subjects is 54%. The sample sizes required for future studies are modest and achievable.

Keywords: cough; acute cough; upper respiratory tract infection; Leicester Cough Questionnaire; Leicester Cough Monitor

INTRODUCTION

Acute cough caused by upper respiratory tract infection (URTI) is the most common reason why patients seek medical attention (1). It can be disruptive to the individual and is often associated with absence from work and lost productivity (2–4). More than \$3 billion is spent on over-the-counter cough and cold remedies each year in the United States (5). The efficacy of antitussive

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Acute cough caused by upper respiratory tract infection is a common reason for consulting a doctor. In studies of antitussive therapy, cough severity can be assessed with cough visual analog scales, health status measures, and 24-hour cough frequency monitors.

What This Study Adds to the Field

This study investigated the serial changes in cough visual analog scales, Leicester Cough Questionnaire score, and objective cough frequency and determined sample sizes required to detect clinically important changes. Cough frequency was significantly raised at baseline and there was a significant reduction in cough frequency and improvement in subjective cough severity outcomes over a 9-day period. The smallest change in 24-hour cough frequency perceived by subjects was a 54% change from baseline. The sample sizes required for future studies are modest and achievable.

medications has recently been questioned by the American College of Chest Physicians cough guidelines and the findings of a metaanalysis (6, 7). There is a pressing clinical need to develop effective antitussive drugs.

The severity of cough is thought to be determined by the frequency of coughs, their intensity, and the impact on health status (8). Assessment of cough severity can be performed using global measures, such as visual analog scales (VAS), or with tools measuring the individual components, such as recently developed cough frequency monitors (9, 10). The impact of cough on health-related quality of life can be assessed with health status questionnaires. Little is known about the severity of cough in URTI particularly that assessed with objective tools, such as cough frequency monitors. Furthermore, there is a paucity of longitudinal studies investigating cough severity and the natural history of URTI. A better understanding of the severity of cough in URTI will facilitate clinical interpretation of studies evaluating antitussive therapy. The aim of this study was to investigate longitudinal cough frequency and other measures of cough severity in URTI, evaluate the magnitude of change important to patients, and determine sample sizes necessary for future clinical studies. Some of the results of this study have been previously reported in the form of an abstract (11).

METHODS

Subjects

Healthy volunteers with cough caused by URTI of less than 10 days' duration were recruited using advertisement posters or referred by their general practitioner during a 15-month period spanning two cold

seasons (January 2010 to April 2011). Subjects with chronic cough, lung disease, current smoking history, symptoms suggestive of bacterial infection, or those taking angiotensin-converting enzyme inhibitor, antihistamine, or antitussive medications were excluded. All subjects gave informed consent and the study was given ethical approval (East London and the City Research Ethics Committee 10/H0703/6).

Cough Frequency Monitoring

Objective 24-hour cough frequency (CF₂₄) was recorded using the Leicester Cough Monitor (LCM), a validated ambulatory cough monitoring system that has been used in randomized controlled trials of therapy for patients with chronic cough (12–15). Briefly, the LCM consists of a MP3 sound recording device (Philips LFH0662/LFH0865, Philips, Amsterdam, The Netherlands), external microphone (Philips LFH9173/Olympus ME-15, Olympus, Tokyo, Japan), and automated cough detection software that requires minor operator input for calibration. Cough frequency was determined by counting all cough events individually, whether occurring in isolation or within coughing bouts. Cough bouts were defined as periods of continuous coughing, with pauses of less than 2 seconds (16). Subjects were instructed to resume normal daily activities in their own environment during cough monitoring. Further details of the LCM and the cough detection algorithm have been described elsewhere (15, 17). CF₂₄ was expressed as the average number of coughs per hour over a 24-hour period. Cough bouts were expressed for 24-hour periods.

Questionnaires

Cough-specific, health-related quality of life was assessed with the Leicester Cough Questionnaire (LCQ-acute), a 19-item questionnaire that has been validated in acute and chronic cough (18, 19). The overall score ranges from 3–21 with a higher score indicating a better quality of life. Subjective cough severity was assessed with a 100-mm cough VAS. Change in cough between visits was assessed with the Global Rate of Change Questionnaire (GRCQ), which was used to estimate clinically important changes in cough outcome parameters at visit 2 (20). The response scale ranged from –7 (a great deal worse) to +7 (a great deal better) and the scores were categorized as no change (–1,0,+1), small change (–2,–3,+2,+3), moderate change (–4,–5,+4,+5), or large change (–7,–6,+7,+6) accordingly.

Protocol

Subject characteristics and symptoms at baseline were recorded. Subjects underwent objective CF₂₄ monitoring at three time points during their illness: visit 1 (recruitment); visit 2 (visit 1 + 4 d); and visit 3 (visit 1 + 8 d). Subjects also completed LCQ and cough VAS at each visit and the GRCQ at visit 2. Cough frequency monitoring was commenced at a similar time of day for each visit. Subjects were instructed to refrain from taking antitussive drugs throughout the study period.

Analysis

SPSS version 19 (IBM, New York, NY) and Prism version 5 (GraphPad, San Diego, CA) were used for statistical analysis. Appropriate parametric or nonparametric tests were applied depending on data distribution. Cough frequency data were log-transformed to achieve normal distribution if appropriate. The upper limits of normal cough frequency in females and males were determined from a previous study, five and two coughs per hour, respectively (21). GRCQ scores were converted to absolute numbers (i.e., when the change was negative, the sign was reversed as was the sign of the corresponding change in VAS, LCQ, and CF₂₄ between visits) (20). The smallest clinically important changes in CF₂₄, LCQ, and VAS were those corresponding to a small change in GRCQ score. The determinants of 24-hour frequency at baseline (visit 1) and change in cough frequency (visits 1–2) were evaluated by univariate analysis of sex, duration of cough, VAS, and LCQ. A longitudinal measure of cough frequency, LCQ, and VAS from visits 1–3 was determined by calculating the area under the curve (AUC) for each subject and dividing by the duration of the study. Sample sizes were calculated using G*Power version 3.1.2 (Faul, Kiel, Germany) to detect the smallest clinically important change (between visits 1 and 2) for both baseline and AUC outcome parameters. Sample-size calculations based on AUC data accounts for change in cough severity in addition to natural recovery. Sample sizes were also determined by a responder analysis between visits 1 and 2 using Fisher exact test. A responder was defined as a subject whose cough improved greater than the smallest clinically important change. The predictive value of baseline LCQ, cough VAS, and cough frequency during the first hour (CF₁) for identifying subjects with low CF₂₄ rates (≤ 10 coughs/h) was assessed by plotting receiver operating characteristic (ROC) curves and calculating the AUC, sensitivity, specificity, negative predictive value, and positive predictive value for each screening tool. A high sensitivity for identifying low-frequency coughers was considered desirable.

RESULTS

A total of 33 subjects (21 female) were included in the final analysis. The reasons for excluding subjects at screening are given in Figure 1. Baseline subject characteristics are given in Table 1.

Natural Course of Acute Cough

The mean $\pm$ SD time from onset of cough to visit 1 was 4.1 ± 2.5 days. Geometric mean $\pm$ log SD CF₂₄ at baseline was 14.9 ± 0.4 coughs per hour. The median (interquartile range [IQR]) number of cough bouts in 24 hours at baseline was 85 (39–195) bouts. Cough-specific quality of life was impaired at baseline; median (IQR) LCQ score was 14.3 (11–18.1). There was a significant reduction in cough frequency, cough bouts, and VAS from visits 1–3, and improvement in health status (Figure 2).

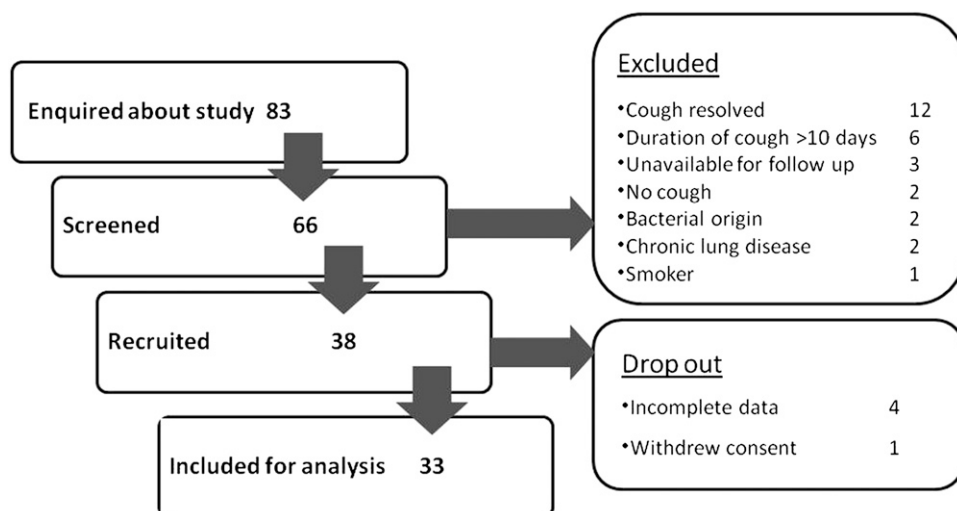


Figure 1. Subject recruitment flow chart.

TABLE 1. BASELINE CHARACTERISTICS

Characteristic	Value
Age, yr	31 (23–37)
Male:Female, n	12:21
Smokers, %	0
Cough duration to presentation, d	4.1 $\pm$ 2.5
Rhinorrhoea, %	82
Sneezing, %	82
Headache, %	69
Sore throat, %	67
Colored sputum, %	50
Clear sputum, %	33
Aches and pains, %	31
Tiredness, %	31
Fever, %	27
Facial pain, %	15
LCQ score	14.3 (11.0–18.1)
Cough VAS, mm	46.0 (32.5–58.0)
CF ₂₄ , coughs/h*	14.9 $\pm$ 0.4
Cough bouts/24 h	85 (39–195)

Definition of abbreviations: CF₂₄ = 24-hour cough frequency; LCQ = Leicester Cough Questionnaire; VAS = visual analog scale.

Data presented as median (interquartile range), mean $\pm$ SD, n, or %.

*Geometric mean $\pm$ log SD.

The geometric mean $\pm$ log SD CF₂₄ at visit 2 and 3 was 8.8 $\pm$ 0.5 (41% reduction from baseline) and 3.3 $\pm$ 0.7 coughs per hour (78% reduction from baseline), respectively. The median (IQR) coughs per bout at visits 1–3 were 2.7 (2.3–3), 2.7 (2.2–3), and 2.5 (2.1–2.9) coughs, respectively ($P = 0.07$, visits 1–3). Cough frequency decreased from visit 1 to visit 2 in 73% of patients and was unchanged or increased in the remainder. In subjects whose cough frequency decreased from visit 1 to visit 2, the magnitude of change in cough frequency was not associated with duration of cough ($P = 0.72$), baseline LCQ ($P = 0.36$), baseline cough VAS ($P = 0.10$), or baseline cough frequency ($P = 0.80$). There were no significant differences in baseline characteristics or cough severity between subjects whose cough improved and deteriorated between visits. At visit 3, 52% of subjects still had cough frequency above normal limits. The geometric mean $\pm$ log SD AUC per day for cough counts and median (IQR) AUC for LCQ and VAS were 248 $\pm$ 0.43 coughs, 16.6 (14.7–19.3) and 26 (18–43) mm, respectively.

Relationship between Subjective and Objective Cough Outcome Measures in Acute Cough

There was a significant relationship between objective cough frequency and LCQ and cough VAS at visits 2 and 3 but not at visit 1 (Table 2). There was also a significant correlation between change in cough frequency and change in LCQ and cough VAS (Table 2).

Determinants of Cough Frequency

Female subjects coughed more frequently than men (geometric mean cough frequency AUC 309 vs. 168 coughs; mean fold difference 1.8; 95% confidence interval, 0.3–3.4; $P = 0.022$). AUC cough severity VAS and LCQ were similar in both sexes ($P = 1.0$ and 0.9, respectively). The relationship between age and cough outcome measures was not assessed because of the narrow age range of subjects. There was no significant relationship between cough frequency and duration of cough ($P = 0.16$), VAS ($P = 0.85$), LCQ ($P = 0.28$), or presence of other URTI symptoms at presentation, such as fever and myalgia ($P = 0.16$ –0.95). There was no difference in LCQ or VAS in subjects with and without noncough URTI symptoms ($P = 0.05$ –0.94). A total

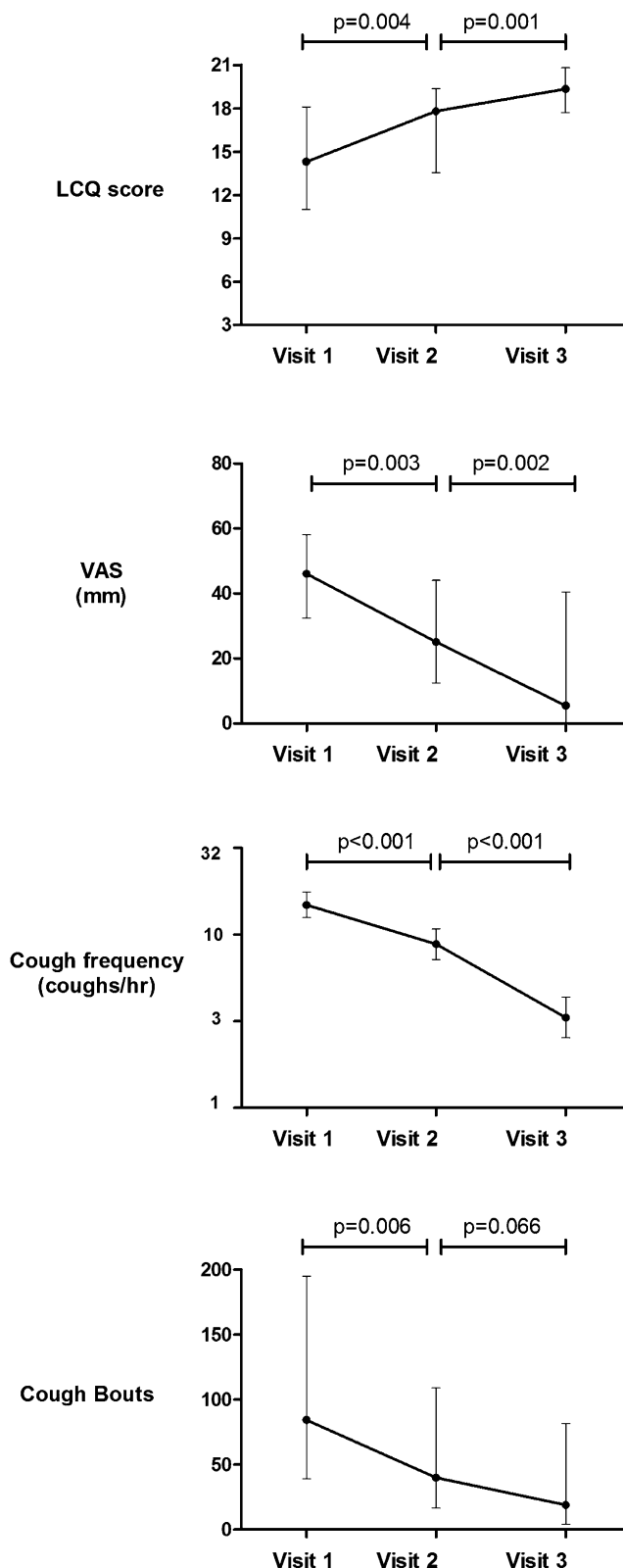


Figure 2. Longitudinal changes in quality of life, subjective cough severity, and objective 24-hour cough frequency. Leicester Cough Questionnaire (LCQ), cough visual analog scale (VAS), and cough bouts data presented as median (interquartile range); cough frequency data presented as geometric mean (SEM).

TABLE 2. RELATIONSHIP BETWEEN SUBJECTIVE AND OBJECTIVE MEASURES OF COUGH SEVERITY IN ACUTE COUGH

	Cough Frequency (CF_{24} , Cough Bouts)			Δ Cough Frequency (CF_{24} , Cough Bouts)	
	Visit 1	Visit 2	Visit 3	Visits 1–2	Visits 2–3
LCQ	–0.23, –0.23	–0.48,* –0.46 [†]	–0.63, [‡] –0.62 [‡]		
VAS	0.03, 0.09	0.42, [†] 0.59 [‡]	0.69, [‡] 0.75 [‡]		
Δ LCQ				–0.55, [†] –0.56*	–0.62, [‡] –0.57*
Δ VAS				0.51, [†] 0.45 [†]	0.66, [‡] 0.70 [‡]

Definition of abbreviations: CF_{24} = 24-hour cough frequency (efforts/h); cough bouts = number of coughing bouts in 24 hours;

LCQ = Leicester Cough Questionnaire; VAS = visual analog scale.

Data presented as correlation coefficients.

* $P < 0.01$.

[†] $P < 0.05$.

[‡] $P < 0.001$.

of 33% of subjects had baseline CF_{24} rates less than or equal to 10 coughs per hour. Both LCQ and cough VAS score at baseline were poor at identifying low-frequency coughers; the AUC of the ROC curves for LCQ and VAS were 0.61 and 0.56, respectively. The geometric mean $\pm$ log SD CF_1 was 23.8 ± 0.4 coughs per hour. The AUC of the ROC curve for CF_1 to detect low-frequency coughers was 0.86. A threshold of CF_1 less than 20.5 coughs per hour had a sensitivity and specificity of 91% and 77%, respectively, for predicting low CF_{24} . The sensitivities and specificities for a range of CF_1 thresholds are listed in Table 3.

Sample-Size Calculations for Future Studies

In patients reporting a small change in GRCQ at visit 2, the change in CF_{24} , LCQ score, and cough VAS was a 54%, 2- and 17-mm change from baseline, respectively (Figure 3). The geometric mean $\pm$ log SD cough frequency for these patients at visits 1 and 2 were 24.2 ± 0.4 and 12.6 ± 0.4 coughs per hour, respectively (mean fold difference 1.9; 95% confidence interval, 1–3.7; $P = 0.049$). The number of subjects required for a parallel group study design to demonstrate a 54%, 2- and 17-mm change in CF_{24} , LCQ, and VAS from visit 1 to 2 (i.e., a change from baseline) with 80% power (α level [α] of 0.05) were 26, 50, and 22 per group, respectively. The number of subjects required for a parallel group study design to demonstrate a 54%, 2- and 17-mm change in AUC (i.e., a change in addition to that with natural recovery) for CF_{24} , LCQ, and VAS with 80% power ($\alpha = 0.05$) were 27, 51, and 25 per group, respectively. Responders were defined as patients whose cough frequency, LCQ, and VAS reduced by greater than or equal to 54%, 2- and 17-mm, respectively, between visits 1 and 2. A total of 42%, 52%, and 55% of subjects responded between visits 1 and 2 (for cough frequency, LCQ, and VAS, respectively). The sample sizes required to detect an additional 20%, 30%, and 40% responders are presented in Table 4.

DISCUSSION

We have reported longitudinal changes in cough frequency, health status, and cough VAS in subjects with acute cough caused by URTI. Cough frequency, assessed objectively with CF_{24} monitors, was increased at baseline. Female subjects coughed more frequently than males. A significant reduction in cough frequency was seen in all subjects in the second week after onset of cough. No clinical characteristic predicted the magnitude of change in cough frequency. There were also significant improvements in health status and cough VAS. This is the first study to estimate the clinically relevant change in cough frequency, LCQ, and VAS in URTI; a 54%, 2- and 17-mm change.

The natural history of cough associated with URTI was characterized by a reduction in cough frequency and cough bouts in most patients, as expected. The reduction in cough frequency between study visits 1 and 2 was 41%, consistent with a rapidly changing condition. In a subgroup of patients (27%), cough frequency increased or was unchanged between visits 1 and 2, before decreasing at visit 3. This observation could have implications for evaluating data from clinical trials of antitussive therapy. A significant mismatch of the number of subjects with worsening cough in the initial phase of illness, in either the placebo or active intervention arms, could lead to misleading interpretation of data. There were no clinical characteristics at baseline, such as duration of cough, which prospectively identified subjects whose cough worsened. The proportion of subjects whose cough worsens during initial assessment should be reported in trials of antitussive therapy to ensure that subject groups are well matched in this respect.

Few studies have evaluated objective cough frequency in subjects with URTI. A recent study by Sunger and coworkers (22) investigated cough frequency over 2 consecutive days in subjects with URTI. Coughs were counted manually. The baseline cough frequency (12.1 coughs/h) was similar to our finding. There were some important differences between our study and that of Sunger and coworkers. We investigated cough frequency over a 9-day period compared with 2 days and included more serial assessments. We investigated the clinically important change in cough frequency and other outcome parameters, allowing us to determine the sample size for future studies with more confidence. Furthermore, we also assessed the longitudinal changes in cough bouts and health status. Cough bouts reduced significantly between visits 1 and 2 and approached significance between visits 2 and 3. In contrast, cough frequency reduced significantly during both intervals. The relationship between health status and cough frequency and bouts was comparable. Kuhn and coworkers (23) assessed the efficacy of the expectorant guaifenesin in URTI in 1982. Cough frequency was measured on 2 consecutive days, earlier from the onset of cough

TABLE 3. PREDICTIVE VALUE OF FIRST-HOUR COUGH FREQUENCY FOR DETECTION OF LOW-FREQUENCY 24-HOUR COUGH COUNTS

CF_1 Threshold (Coughs/h)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
<16.5	64	86	70	83
<19.0	82	82	69	90
<20.5	91	77	67	94

Definition of abbreviations: CF_1 = cough frequency in the first hour; NPV = negative predictive value; PPV = positive predictive value.

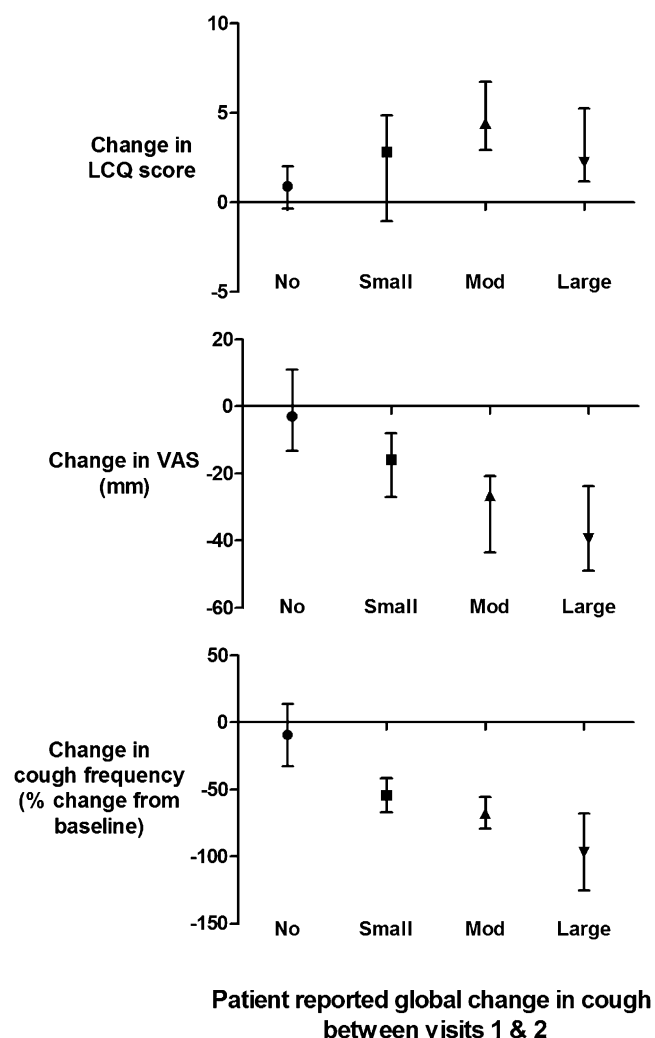


Figure 3. Clinically important changes in Leicester Cough Questionnaire (LCQ) (*top*), cough visual analog scale (VAS) (*middle*), and 24-hour cough frequency in acute cough (*bottom*). LCQ and cough VAS data presented as median (interquartile range); cough frequency data presented as geometric mean (SEM). The small change in a cough outcome parameter is considered the minimal important difference.

compared with our study (2 vs. 4 d). This is likely to explain the higher cough frequency reported at baseline by Kuhn and coworkers; 34 coughs per hour in the placebo group. Cough frequency on the fourth day from onset of cough, however, was similar to our study (16 coughs/h). There were also important differences in the cough detection methodology. A voice-activated tape recorder was used, in contrast to continuous MP3 sound recording in our study. Subjects were also confined to a study room in the study by Kuhn and coworkers; the LCM used in our study allowed ambulatory recordings. In a trial of dextromethorphan in subjects with URTI, Pavesi and coworkers (24) assessed cough frequency using an automated cough detection system. Cough frequency was recorded over a shorter duration (4 h) in a confined environment.

In subjects reporting a small subjective change in cough severity, the observed change in cough frequency over a 4-day period was substantial, a 54% change. Such a magnitude of change in cough frequency is noteworthy because it relates to subjects reporting only a mild degree of change in their cough. This has implications for clinical trials of antitussive therapy, particularly those conducted over several days. In our study this change

was observed with natural recovery alone. We did not investigate the placebo effect that is often seen in cough studies (25). Antitussive therapies should therefore aim for greater than 54% reduction in cough frequency. This may be difficult to achieve as suggested by the findings of Pavesi and coworkers (24) (13% reduction in cough frequency with dextromethorphan). Further studies should explore the potential to evaluate antitussive therapy over a shorter duration, such as single-dose studies where the change in cough frequency with natural recovery is likely to be less marked. We report the smallest clinically important change in VAS in acute cough for the first time, a 17-mm change. The VAS is a widely used, simple, and valid tool for the assessment of global cough severity. Our findings should facilitate clinical interpretation of VAS data. The smallest change in LCQ important to patients was 2, similar to that reported in a previous study (18).

The purpose of estimating the smallest change in cough outcome parameters perceived important to patients, often referred to as the minimal important difference (MID), was to determine sample sizes for future studies (20). Our methodology was similar to that used in other conditions to define MIDs, but we advise caution in interpreting our data as the MID because cough outcome parameters rapidly change over time with natural recovery in URTI. We determined clinically important changes in cough outcome parameters at visit 2, not visit 3. We envisaged that cough would have resolved or be near resolution in most subjects by visit 3, which would make the assessment of the MID difficult at visit 3. Further studies should assess whether the magnitude of clinically important changes in outcome parameters are influenced by the time course of illness. We estimated the sample sizes required for future parallel group studies to detect a clinically significant change in cough frequency, LCQ, and VAS. The sample size was greatest for LCQ. This reflects the relatively smaller magnitude of change required for the LCQ compared with that for cough frequency. Our estimation of the sample size for cough frequency is consistent with that reported by Sunger and coworkers (22). In contrast to Sunger and coworkers, we were also able to determine sample-size estimates for LCQ and VAS outcome measures. A strength of our sample-size calculation is that we used an anchor-based method to determine the magnitude of change that was clinically important to patients. The advantage of using AUC data for sample-size calculations is that they assess change in addition to natural recovery. The sample sizes were larger with the responder analysis, consistent with previous studies using responder analysis (26). The limitations of responder analysis are its reduced power relative to that of continuous outcome measure scales and the arbitrary nature of the definition of a response; both are thought to increase the sample size (26). We investigated the factors that may influence the magnitude of change in cough frequency because this affects the sample-size calculation. Although we were underpowered to study this with confidence, none of the parameters assessed predicted the change in cough frequency. We do not propose a crossover design for future studies because URTI is a rapidly changing condition and because our data suggest that the sample size for parallel group studies is achievable, but others have suggested this may be possible (22).

We evaluated predictors of CF₂₄ at baseline. A simple, brief screening tool that identifies patients with low CF₂₄ may be useful for research studies and clinical trials to facilitate recruitment of patients with a clinically significant cough frequency. CF₁ was the best predictor of CF₂₄. Subjective assessments of cough severity were poor predictors of cough frequency. CF₁ less than 20.5 coughs per hour had a 91% sensitivity to identify low cough frequency. A limitation of this threshold is that approximately one-third of subjects are potentially misclassified as

TABLE 4. SAMPLE-SIZE CALCULATIONS

	Change from Baseline (Visits 1–2)	AUC (Visits 1–3)	Responder Analysis (Additional Response Rate)		
			20%	30%	40%
Cough frequency	26	27	102	48	28
LCQ	50	51	101	43	22
VAS	22	25	98	41	20

Definition of abbreviations: AUC = area under the curve; LCQ = Leicester Cough Questionnaire; VAS = visual analog scale.

Sample sizes are per group for a parallel study design. Sample sizes are calculated with 80% power and alpha level of 0.05 to demonstrate smallest clinically important change: 54%, 2- and 17-mm change in 24-hour cough frequency, Leicester Cough Questionnaire (LCQ) and visual analog scale (VAS), respectively.

having a low-frequency cough and therefore excluded from studies (67% positive predictive value). Further evaluation of CF₁ as a screening tool in clinical trials is needed. At the end of our study, 52% of subjects had abnormally raised cough frequency, suggesting that cough frequency from URTI may take some weeks to return to baseline in a significant number of subjects. Jones and Stewart (27) previously reported that cough (assessed subjectively) persisted 2 weeks after onset in a similar proportion of subjects (58%).

Health status was severely impaired in cough associated with URTI, affecting all domains. This is consistent with previous studies (18, 28). The degree of health status impairment was comparable with patients with chronic cough (29). In contrast to chronic cough, health status was transiently impaired, returning to near normal levels as patients improved. The relationship between health status and VAS with cough frequency was best at visits 2 and 3. The correlation was moderate, consistent with other studies, suggesting that other factors such as cough intensity may be important determinants of cough severity (16, 29, 30). The relationship between subjective and objective parameters was poor at visit 1. It is possible that symptoms, such as rhinorrhea, headache, sleep disturbance, and those causing disruption to daily activities may have had a greater impact on general health status at the onset of illness compared with cough. The relationship between longitudinal changes in subjective and objective measures of cough was more consistent than that with cross-sectional assessments. The VAS performed better than the LCQ in subjects reporting a large change in their cough severity. However, the relationship with baseline cough frequency was better with LCQ compared with VAS. The reasons for this are unclear. Further studies with larger number of subjects are needed to investigate whether there are important differences in the performance of subjective outcome tools.

There are limitations to this study. Although the cough frequency of the overall group reduced significantly over the duration of the study, a significant proportion of subjects still had abnormally raised cough frequency at visit 3. Ideally, further assessments up to the point of resolution of cough or when a plateau in cough frequency was observed would have been preferable. Additional assessments during the early phase of illness would also have been desirable. Our study population was young and did not have comorbidity. It is therefore not known if cough frequency in older subjects differs; this needs further investigation. However, in chronic cough, there is no significant relationship between cough frequency and age (12). The duration of cough at recruitment was not identical for all subjects; this could have had an impact on the degree of change in cough severity between study visits. Our study was underpowered to perform a subanalysis of patients with identical duration from onset of cough. The recruitment of patients with an identical duration of cough in the early phase of illness is challenging because of the unpredictable incidence and rapidly changing nature of

acute cough. However, the impact of this limitation may be less marked in our study, because we found no association between the duration of cough and change in cough frequency. The cause of acute cough was not investigated in our study. It is possible that differences in the type of virus may impact the severity of cough. Studies using induced viral URTIs may address this. It is also possible that noninfectious causes may have been responsible for acute cough in some subjects.

It is possible that inaccuracies in the LCM cough detection software may have impacted our findings because the LCM was validated in subjects with chronic cough. The cough recordings in the current study were ambulatory and in the subjects' own environment, similar to previous studies in chronic cough (29). Furthermore, the cough frequency rates observed in our study were similar to those in another study of acute cough in which coughs were counted manually (22). Our definition of low cough frequency was based on an arbitrary threshold of less than 10 coughs per hour. We chose this because it was less than the average for subjects with URTI but higher than that reported for healthy subjects (21). Our analysis should be considered preliminary and further thresholds evaluated in larger studies. We only investigated the potential for the CF₁ to predict CF₂₄ and both measurements were obtained from the same recording. These limitations should be addressed by investigating longer-duration recordings conducted separately from the 24-hour recording. We did not evaluate cough intensity in our study. This is not currently possible in an ambulatory setting. There is a pressing need to develop tools to measure cough intensity. We reported clinically important changes for subjects who reported a small change in cough severity. It is possible that the changes differed between those who improved and those who deteriorated; our study was underpowered to assess this. Lastly, it is possible that subjects may have associated the change in cough assessed with the GRCQ more closely with their cough severity at the follow-up visit compared with baseline (31). The short interval between study visits, 4 days, should have minimized recall bias but this should be addressed in future studies by determining change prospectively.

In conclusion, a number of valid tools are available to assess cough severity in acute cough secondary to URTI. CF₂₄ monitoring is a practical, objective, and responsive outcome parameter. Cough frequency in patients with URTI was significantly raised. The smallest important change in CF₂₄ was 54%. Health status was significantly impaired because of cough in URTI and returned to near normal levels with recovery. The relationship between cough frequency and health status was weak to moderate, suggesting that subjective and objective outcome tools should be used to assess cough comprehensively. The sample sizes required for parallel group studies for a range of outcome parameters are modest and achievable. Our data will facilitate the design of future trials of therapy.

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