Online Supplement of Expanded Methods and Questionnaires

Title: Predicting worsening asthma control following the common cold

MATERIALS AND METHODS

Study Population

The PAX study was a multi-center prospective cohort study that recruited subjects with mild to moderate persistent asthma from January 2005 to April 2006. This study recruited subjects from the Long Acting Beta Agonist Response by Genotype (LARGE) parent study performed by the Nation Institute of Health Asthma Clinical Research Network (ACRN). Men and women ages 18 and older with a clinical history of asthma, an $FEV_1 \geq$ 40% predicted (50% if on inhaled corticosteroids), bronchial hyper-responsiveness or reversible airway obstruction, and a total lifetime smoking history of < 10 pack-years were recruited. Patients were excluded if they were using > the equivalent of 1000 μg per day of inhaled fluticasone, or if they had a lung disease other than asthma, vocal cord dysfunction, significant medical illness that was unstable, respiratory tract infection or significant asthma exacerbation in the last 6 weeks, or life-threatening asthma requiring intubation in the past 10 years.

Study Design

At study entry, informed consent was obtained and this was followed by acquisition of demographic information, completion of questionnaires, spirometry, blood draw for measurement of serum IgE level, and administration of the entry mini-ACQ questionnaire. Cold status was evaluated daily by self-report and when a subject reported

having a cold, they were instructed to contact the study coordinator so that post-cold asthma control could be assessed with a mini-ACQ by phone interview approximately 7 days after the cold onset (Post-cold day 7 mini-ACQ) and 14 days after the cold onset (Post-cold day 14 mini-ACQ). Since asthma control and the mini-ACQ may fluctuate over time we acquired periodic mini-ACQ scores (approximately every 8 weeks) to serve as a recent Pre-cold mini-ACQ score for comparison to subsequent cold episode mini-ACQ scores. The differences between the Post-cold day 7 and day 14 mini-ACQ scores and the Pre-cold mini-ACQ score were used to define the change in asthma control following a cold. The protocol was reviewed and approved by the ACRN steering committee, a National Heart, Lung, and Blood Institute (NHLBI) Protocol Review Committee, and a NHLBI Data Safety Monitoring Board, and each centers' Institutional Review Board.

Cold Episode

Cold episodes were identified using the daily diary cards and logs maintained by the study coordinators. On the daily diary cards, the subjects were instructed to answer the cold question "Do you have a cold today?" [1]. An affirmative answer was considered the date of onset of a cold episode and referred to as Day 1 of the cold. If the daily diary data was incomplete, a cold episode was also identified using a cold tracking log that was completed by the study coordinators when the subject notified the coordinator of a cold and by the presence of WURSS-21 cold scores. Completion of a cold episode required the subject to answer the cold question "no" for two consecutive days. Following a cold episode the subject continued to answer the daily cold question, therefore each subject

could contribute data on more than one cold episode. Length of cold was calculated as the total number of days that the subject answered the cold question "yes". If this data was not available, the length of the cold was ascertained from the study coordinators' log. Since we were interested in identifying colds prospectively, we excluded any cold episodes with an onset date within 14 days of subject entry into the study. We were also interested in the season in which the onset of the cold episode occurred. The seasons were defined as November 1 through February 28, March 1 through June 30, and July 1 through October 31.

Asthma Control

Asthma control was assessed using the Asthma Control Questionnaire without lung function, referred to as the mini-ACQ [2]. The mini-ACQ has a one-week recall and consists of 6 questions with 7-point Likert scale answers related to asthma symptoms (5 questions) and short-acting bronchodilator use (1 question) (Supplement Figure S1 and S2) [2-4]. The mini-ACQ score is the mean of all 6 questions (range of 0 to 6) with higher scores indicating worse asthma control and the minimally important difference (MID) is a change of 0.5. The mini-ACQ was completed periodically over the course of the study, at approximately 8-week intervals, as well as 7 days and 14 days after cold onset. The mean time intervals of Pre-cold mini-ACQ to onset of cold, onset to Post-cold day 7 mini-ACQ, and onset to Post-cold day 14 mini-ACQ were 39.0 ± 35.4, 7.8 ± 2.3, and 15.0 ± 4.4 days respectively.

Cold Symptoms

The Wisconsin Upper Respiratory Symptom Survey (WURSS-21) is a quality of life assessment that measures the health-related affects of the common cold [5, 6]. The WURSS-21 questionnaire was approved for use on 9/29/05 and was administered daily after the onset of a cold and consists of 21 questions with 7-point Likert scale answers that related to global illness (1 question), cold symptoms (10 questions), functional impairment (9 questions) and global change (1 question) (Supplement Figure S3). The WURSS-21 score is the mean of the first 20 questions (range of 0 to 140) with higher scores indicating more symptoms and the MID is a change of 9.48 [5]. The initial WURSS-21 score was the first WURSS-21 score recorded during a cold episode and the peak WURSS-21 score was the highest score of all daily values. The summary WURSS-21 scores were the cumulative sum of the corresponding daily WURSS-21 scores. To obtain WURSS-21 scores in asthma subjects without a cold, subjects with stable asthma symptoms were administered the WURSS-21 for 14 consecutive days.

Rescue Albuterol Use

To determine if rescue albuterol use was associated with a change in post-cold asthma control we tracked the number of open label inhaled albuterol puffs (90 micrograms/puff) following the cold onset. Rescue albuterol puffs were recorded on the diary as "total number of puffs during the last 24 hours (Do not record preventive use)". The baseline rescue albuterol puffs per day was calculated as the mean puffs per day for the 21 days prior to the first day of the cold onset. For the first 7 days of the cold, the daily change in rescue albuterol puffs per day from baseline was calculated (daily value minus baseline value). The peak value was defined as the daily value with the greatest increase from

baseline. The summary rescue albuterol puffs per day values were the cumulative sum of the corresponding daily values.

Historical Cold Characteristics

The PAX Cold Questionnaire was used to assess historical cold characteristics and consisted of four questions related to prior cold frequency every year (1 question), severity of colds (1 question), the frequency of cold-induced asthma symptoms (1 question), and the severity of their cold-induced asthma symptoms (1 question) (Supplement Figure S4). The PAX Cold questionnaire was approved for use on 4/27/06 and was administered to those subjects with a cold episode. The first question quantified the number of colds every year and the last three questions had Likert scale answers.

Measurement of Clinical Characteristics and Time Intervals

Pre- and post-bronchodilator spirometry and methacholine challenge testing were performed with KoKo spirometers (PDS Instrumentation Inc., Louisville, CO) and Quantum Research software (Louisville, CO) according to American Thoracic Society guidelines [7]. Blood samples for total serum IgE concentrations were collected at study entry and Immunocap measurement was performed at Specialty Laboratories (Valencia, CA) with a sensitivity of 2.0 international units (IU)/ml. Total serum IgE concentrations reported as < 2.0 IU/ml were assigned a value of 1.0 IU/ml for analytic testing (one value in Non-cold and Cold Cohort). Atopic status was defined as greater than or equal to one positive skin test. Allergens used in the testing panel were mite mix, cockroach mix, mouse, rat, *Penicillium*, *Alternaria*, *Aspergillus*, *Cladosporium*, cat and dog. Skin testing

was performed with a Multi-Test II device (Lincoln Diagnostics, Inc.) and a valid test required at least a 3 mm wheal with surrounding erythema to the histamine positive control. For each allergen the skin test was considered positive if the wheal exceeded that elicited by the negative control (diluent) by 3 mm with documented erythema. Prior smoking status was assessed by a self-report.

To determine if concurrent treatment medications associated with a change in post-cold asthma control we noted the treatment medications at the time of the cold onset date. The main study was a crossover design and consisted of a Run-in phase, Stage 1 active treatment with study drug, Stage 1 run-out, Stage 2 active treatment with study drug not used in Stage 1, and Stage 2 run-out. Cold episodes in the main study could have occurred while receiving one of three study drug regimens: beclomethasone 240 micrograms twice a day plus albuterol rescue (Run-in, Stage 1 run-out, and Stage 2 run-out phases); beclomethasone 240 micrograms twice a day plus salmeterol 50 micrograms twice a day plus atrovent rescue (Stage 1 active treatment); and beclomethasone 240 micrograms twice a day plus placebo twice a day plus atrovent rescue (Stage 2 active treatment). The study entry date was defined as the earlier date of the first daily diary entry or first mini-ACQ entry and the study termination date was defined as the latest date of the last daily diary entry or the last mini-ACQ entry (before May 1, 2006). Follow-up time was calculated as the total number of days between and inclusive of the study entry and termination dates.

Cold-induced Asthma Exacerbation

Criteria for a cold-induced asthma exacerbation included meeting any one of the following criteria during the cold episode: (1) treatment of asthma symptoms with inhaled, oral, or parenteral glucocorticoids, (2) asthma symptoms plus an increase in rescue albuterol of > 8 puffs above baseline for 2 consecutive days or asthma symptoms plus an increase in rescue albuterol of > 16 puffs above baseline in 24 hours, (3) unscheduled health care contact including office visit or obtaining a prescription for antibiotics, (4) emergency department visit or hospitalization for asthma. Cold-related asthma exacerbations were identified by review of daily diaries, and all adverse events, significant asthma exacerbations, and concomitant medications (updated at each office visit).

Statistical Analysis

For comparison of the Cold cohort to the Non-cold cohort and the No Exacerbation to the Exacerbation cohort, continuous and categorical variables were examined using an independent-groups t-test and a chi-squared or Fisher's exact test where appropriate. The total serum IgE concentrations were $\log_{10}$ transformed to achieve a normal distribution prior to all analyses and results were reported as geometric mean and coefficient of variation. The domains assessed by the WURSS-21 questionnaire are not specific to the common cold and could be elevated due to asthma symptoms [5]. To determine the extent that asthma symptoms increased the WURSS-21 scores we compared the WURSS-21 scores in asthmatics with and without a cold. For subjects with a cold, the first cold episode with WURSS-21 data was used. The WURSS 21 scores for each day, the peak score, and the cumulative sum for Days 1-2, Days 1-4, and Days 1-7 were

compared using independent-groups t-tests. To investigate the change in asthma control following a cold, the Pre-cold, Post-cold day 7, and Post-cold day 14 mini-ACQ scores were compared using repeated measures analysis of variance. To investigate the change in rescue albuterol use following a cold, the number of puffs/day at baseline and days 1 through 7 were compared using repeated measures analysis of variance

Covariates associated with the change between Pre-cold and Post-cold day 7 mini-ACQ scores were identified using independent or paired t-test, repeated measures ANOVA, and Pearson's correlation. For all comparisons a p-value of < 0.05 was considered significant. WURSS-21 scores were analyzed using generalized estimating equation (GEE) [8]. GEE allows for the correlation of multiple events from a single person, i.e. colds from the same patient. In addition, GEE does not make assumptions about the distribution of the outcome variable, therefore the quasi-likelihood under the independence model criterion (QIC)u was used to assess model performance for variable selection.

To examine the relationship between covariates available within the first 48 hours of cold onset and the changes in asthma control, two types of multivariable analyses were conducted: 1) models using pre-selected covariates and 2) selection of the best model. For the models using pre-selected covariates, cold characteristics that were associated with a change in asthma control were included with either the Day 1, Day 2, or Sum Day 1-2 WURSS-21 scores. Season of onset and center location were collapsed into fewer categories (season: March-October vs November-February; center location: Eastern vs

Central/Mountain vs Pacific). To find the best model to explain the relationship between cold severity and changes in asthma control, a stepwise variable selection method was utilized. Potential predictors were included in the model if they could be obtained within the first 48 hours of a cold episode, and had a marginal association p-value of ≤ 0.05. Potential predictors were removed from the model if their p-value was > 0.10. The models were ranked on the basis of their QICu scores. When the final model was created, the best correlation structure was selected using the QIC statistic. For all comparisons a p-value of < 0.05 was considered significant. Data were analyzed with SAS 9.1.2 (SAS Institute, Cary, NC) and SPSS 13.0 (SPSS, Chicago, IL).

RESULTS

Characteristics of Subjects with Cold-induced Asthma Exacerbations and Multiple Colds

To identify characteristics that associated with a post-cold asthma exacerbation, we examined the 87 subjects with available exacerbation data, 63 did not have a cold-induced exacerbation and 24 had a least one cold with an exacerbation. The subjects with a cold-induced asthma exacerbation were more likely to be Hispanic, have lower lung function, report a history of more severe and frequent cold-induced asthma symptoms on the PAX Cold Questionnaire, and have longer cold duration (Supplement Tables S1 and S2). Using logistic regression analysis, all of these variables, except race, were associated with an increased risk of a post-cold asthma exacerbation (Supplement Table S3). Although our sample size precluded the use of multivariable analysis, these findings are in agreement with a recent prospective study that identified low lung function (pre-

bronchodilator FEV_1 % predicted) as the most significant predictor of subsequent acute asthma care [9]. Accordingly, asthmatics with low lung function, colds of long duration and a previous history of frequent and more severe cold-induced asthma symptoms may be at increased risk for developing a post-cold asthma exacerbation and at a minimum warrant close clinical monitoring.

We next determined the incidence of cold-induced asthma exacerbations in these 87 subjects. Of the 211 total cold episodes, 64 could not be evaluated for an exacerbation because the colds occurred during the initial phase of the PAX study when exacerbation data were not collected (n=43) or because of incomplete data (n=21). In the remaining 147 cold episodes, there were 27 (18.4%) exacerbations in 24 individuals (3 individuals had 2 exacerbations) for an overall incidence of 0.41 cold-induced exacerbations per subject-year of follow-up. The exacerbation criteria met included: increased oral or inhaled glucocorticoids in 13, an unscheduled health care contact in 13, and an increase in rescue albuterol use in one (Supplement Table S2). To our knowledge none of the subjects with a cold-induced asthma exacerbation visited the emergency department or were admitted to the hospital.

To determine if the changes in mini-ACQ and WURSS-21 scores were higher in asthmatics with a cold-induced asthma exacerbation, we compared the scores in the episodes without and with a cold-induced exacerbation. The cold episodes with an exacerbation demonstrated a significant increase in the Post-cold mini-ACQ 1 and 2, the change between Pre-cold and Post-cold 1 scores, the proportion of cold episodes with a

change in mini-ACQ greater than 0.5, the change between Pre-cold and Post-cold 1 scores, peak WURSS-21 score, and the cumulative Sum Day 1-7 WURSS-21 scores. Although the Day 1, Day 2, and cumulative Sum day 1-2 and Sum Day 1-4 WURSS-21 scores were increased above the MID, this difference was not statistically significant (Supplement Table S2).

Online Supplement References:

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Supplement Table S1. Demographic Characteristics of Exacerbation Cohorts*

	No Exacerbation (n = 63)	Exacerbation (n =24)	p
Female, n (%)	45 (71.4)	20 (83.3)	0.25
Race or ethnicity, n (%)†			0.005
White, non-Hispanic	56 (88.9)	18 (75.0)	
Black, non-Hispanic	5 (7.9)	0 (0)	
Hispanic	1 (1.6)	5 (20.0)	
Other	1 (1.6)	1 (4.2)	
Age, years	39.4 ± 11.6	41.3 ± 12.0	0.49
Subjects per center, n (%)			0.27
Boston	7 (11.1)	4 (16.7)	
Denver	12 (19.0)	3 (12.5)	
Madison	18 (28.6)	3 (12.5)	
San Diego	4 (6.3)	5 (20.8)	
San Francisco	12 (19.0)	3 (12.5)	
Saint Louis	4 (6.3)	2 (8.3)	
Winston-Salem	6 (9.5)	4 (16.7)	
Pre-bronchodilator FEV_1			
Liters	2.79 ± 0.75	2.35 ± 0.77	0.02
% predicted	83.0 ± 14.8	73.4 ± 14.9	0.01
Total serum IgE, IU/ml‡	101.1, 109	78.5, 91	0.40
Atopic, n (%)§	35 (97.2)	15 (93.8)	0.53
Prior tobacco use, n (%)	11 (17.5)	5 (20.8)	0.72
Entry mini-ACQ score‖	0.99 ± 0.75	1.15 ± 0.75	0.39
Entry mini-ACQ > 1.25, n (%)	20 (31.7)	12 (50)	0.12
Follow-up time, subject-years			
Total	48.0	18.9	
Per subject	0.76 ± 0.34	0.79 ± 0.29	0.73
Reported colds per subject, n (%)			0.06
1	36 (57.1)	9 (37.5)	
2	14 (22.2)	8 (33.3)	
3	10 (15.9)	2 (8.3)	
≥4	3 (4.8)	5 (20.8)	
Cold Episodes	1.68 ± 0.91	2.25 ± 1.42	0.08
Cold Episodes per subject-year follow-up	2.81 ± 2.62	2.73 ± 1.05	0.89
PAX Cold Questionnaire responses**			
Colds per year	2.24 ± 1.17	3.59 ± 2.18	0.03
Severity of previous colds	2.93 ± 0.68	3.65 ± 0.70	0.001
Frequency of cold-induced asthma symptoms	3.45 ± 1.10	4.18 ± 0.88	0.02
Severity of cold-induced asthma symptoms	2.83 ± 0.80	3.53 ± 0.80	0.004

* Plus-minus values are means ± standard deviation (SD)

† race, ethnicity, and prior tobacco use were self-reported

‡ reported as geometric mean and coefficient of variation (%), for statistical analysis values were $\log_{10}$ transformed

§ n=36 in No Exacerbation and 16 in Exacerbation cohort

‖ Scores can range from 0 (no symptoms) to 6 (severe symptoms)

** n=42 in No Exacerbation and 17 in Exacerbation cohort

Supplement Table S2. Characteristics of Cold Episodes Without or With an Exacerbation[*]

	No Exacerbation (n = 120)	Exacerbation (n =27)	p
Exacerbations with cold episode, n (%)			
Total		27 (18.4)	
Glucocorticoids		13 (8.8)	
Increased glucocorticoids		10	
Increased glucocorticoids and antibiotics		2	
Increased glucocorticoids and antibiotics and SABA		1	
Unscheduled health care contact		13 (8.8)	
Increased rescue SABA		1 (0.7)	
Emergency department visit or hospitalization		0 (0.0)	
Colds episodes per center			0.31
Boston	17 (14.2)	5 (18.5)	
Denver	23 (19.2)	3 (11.1)	
Madison	34 (28.3)	4 (14.8)	
San Diego	8 (6.7)	5 (18.5)	
San Francisco	21 (17.5)	4 (14.8)	
Saint Louis	6 (5)	2 (7.4)	
Winston-Salem	11 (9.2)	4 (14.8)	
Season with cold episode, n (%)			0.39
November-February	54 (45.0)	15 (55.6)	
March-June	28 (23.3)	7 (25.9)	
July-October	38 (31.7)	5 (18.5)	
Cold episodes per subject-year of follow-up			
November-February[†]	4.65 ± 8.24	4.66 ± 2.89	0.99
March-June[‡]	3.19 ± 6.43	1.44 ± 2.10	0.20
July-October[§]	2.15 ± 2.65	2.29 ± 2.67	0.82
Length of cold, days[‖]	6.5 ± 3.9	10.1 ± 5.2	< 0.001
Rescue albuterol use after cold onset, puffs/day[**]			
Day 1	0.96 ± 1.75	1.65 ± 2.47	0.27
Day 2	0.99 ± 1.89	1.83 ± 2.52	0.21
Peak	2.24 ± 2.37	2.92 ± 2.50	0.39
Sum day 1-2	1.94 ± 3.54	3.48 ± 4.68	0.22
Sum day 1-4	4.28 ± 7.07	7.50 ± 9.29	0.20
Sum day 1-7	6.92 ± 10.69	12.44 ± 15.40	0.15
Mini-ACQ			
Pre-cold[††]	0.81 ± 0.74	0.88 ± 0.17	0.66
Post-cold day 7[‡‡]	1.25 ± 0.91	2.31 ± 0.93	< 0.001
Post-cold day 14[§§]	0.88 ± 0.76	1.93 ± 1.19	0.001
Change between Pre-Cold and Post-cold day 7[‖‖]	0.55 ± 0.73	1.41 ± 1.08	0.002
Change between Pre-Cold and Post-cold day 7 ≥ 0.5, n (%)[‖‖]	36 (45.0)	16 (76.2)	0.01
Change between Pre-Cold and Post-cold day 14 [***]	0.16 ± 0.58	1.09 ± 1.26	0.005
WURSS-21[†††]			
Day 1	37.9 ± 30.0	46.0 ± 35.2	0.50
Day 2	41.1 ± 27.1	60.6 ± 36.0	0.09
Peak	56.7 ± 31.4	82.9 ± 28.9	0.03
Sum day 1-2	79.0 ± 56.1	106.5 ± 67.7	0.22
Sum day 1-4	158.0 ± 105.4	227.5 ±132.0	0.11
Sum day 1-7	233.0 ± 155.6	376.8 ± 201.8	0.03

* Plus-minus values are means ± standard deviation, † n=86 in No Exacerbations and 20 in Exacerbation cohort, ‡ n=91 in No Exacerbations and 23 in Exacerbation cohort, § n=81 in No Exacerbations and 22 in Exacerbation cohort, ‖ n=116 in No Exacerbations and 26 in Exacerbation cohort, ** n=55 in No Exacerbations and 11 in Exacerbation cohort, †† n=118 in No Exacerbations and 27 in Exacerbation cohort, ‡‡ n=81 in No Exacerbations and 21 in Exacerbation cohort, §§ n=80 in No Exacerbations and 19 in Exacerbation cohort, ‖ ‖ n=80 in No Exacerbations and 21 in Exacerbation cohort, *** n=79 in No Exacerbations and 19 in Exacerbation cohort, ††† n=23 in No Exacerbations and 11 in Exacerbation cohort.

Table S3. Characteristics that Associate with a Post-cold Asthma Exacerbation*

Explanatory Variable	Regression Coefficient (β)	Odds Ratio	95% CI	p
Pre-bronchodilator FEV_1†				
Liters‡	-0.88	0.41	0.19-0.88	0.02
% predicted	-0.05	0.96	0.92-0.99	0.01
PAX Cold Questionnaire§				
Colds per year‖	0.53	1.70	1.12-2.56	0.012
Severity of previous colds	1.67	5.01	1.78-14.58	0.002
Frequency of cold-induced asthma symptoms	0.71	2.03	1.09-3.79	0.03
Severity of cold-induced asthma symptoms	1.21	3.35	1.36-8.22	0.008
Length of cold**	0.12	1.13	1.01-1.26	0.03

* Univariate logistic regression analysis with post-cold asthma exacerbation status (yes/no) as dependent variable

† n=87

‡ For every increase in pre-bronchodilator FEV_1 by 1.0 liter we predict a -0.88 decrease in the log-odds of a post-cold asthma exacerbation. Therefore, the odds of a post-cold asthma exacerbation are decreased by 59% for each increase in pre-bronchodilator FEV_1 by 1 liter. A more reasonable change might be 0.25 liter, in which case we predict a -0.22 decrease in the log-odds of a post-cold asthma exacerbation and a decrease in the odds by 20%. Similar interpretation for pre-bronchodilator FEV_1 % predicted.

§ n=59

‖ For every increase in colds by one per year we predict a 0.53 increase in the log-odds of a post-cold asthma exacerbation. Therefore the odds of a post-cold asthma exacerbation are increased by 70% for each increase in colds per year by 1 cold. Similar interpretation for all PAX Cold Questionnaire responses.

** n=83, for every increase in cold duration by one day we predict a 0.12 increase in the log-odds of a post-cold asthma exacerbation. Therefore the odds of a post-cold asthma exacerbation are increased by 13% for each increase in cold duration by one day.

Asthma Clinical Research Network
NIH/NHLBI

PAX FEASIBILITY ASTHMA CONTROL QUESTIONNAIRE

Subject ID: ___ ___ - ___ ___ - ___ ___ ___
Subject Initials: ___ ___ ___ ___
Visit Number: ___ ___ ___
Visit Date: ___ ___ / ___ ___ / ___ ___ (Month / Day / Year)
Coordinator ID: ___ ___ ___ ___ ___ ___

(Subject/Interview completed)

Have you had a cold in the last 14 days? ☐ 1 Yes ☐ 0 No

Please check the box next to the response that best describes how you have been during the <u>past week.</u>

1. On average, during the past week, how often were you woken by your asthma during the night?
   - ☐ 0 Never
   - ☐ 1 Hardly ever
   - ☐ 2 A few times
   - ☐ 3 Several times
   - ☐ 4 Many times
   - ☐ 5 A great many times
   - ☐ 6 Unable to sleep because of asthma

2. On average, during the past week, how bad were your asthma symptoms when you woke up in the morning?
   - ☐ 0 No symptoms
   - ☐ 1 Very mild symptoms
   - ☐ 2 Mild symptoms
   - ☐ 3 Moderate symptoms
   - ☐ 4 Quite severe symptoms
   - ☐ 5 Severe symptoms
   - ☐ 6 Very severe symptoms

3. In general, during the past week, how limited were you in your activities because of your asthma?
   - ☐ 0 Not limited at all
   - ☐ 1 Very slightly limited
   - ☐ 2 Slightly limited
   - ☐ 3 Moderately limited
   - ☐ 4 Very limited
   - ☐ 5 Extremely limited
   - ☐ 6 Totally limited

4. In general, during the past week, how much shortness of breath did you experience because of your asthma?
   - ☐ 0 None
   - ☐ 1 A very little
   - ☐ 2 A little
   - ☐ 3 A moderate amount
   - ☐ 4 Quite a lot
   - ☐ 5 A great deal
   - ☐ 6 A very great deal

Figure S1. Page 1 of PAX Feasibility mini-Asthma Control Questionnaire (mini-ACQ).

5. In general, during the past week, how much of the time did you wheeze?

- ☐ 0 Not at all
- ☐ 1 Hardly any of the time
- ☐ 2 A little of the time
- ☐ 3 A moderate amount of the time
- ☐ 4 A lot of the time
- ☐ 5 Most of the time
- ☐ 6 All the time

6. On average, during the past week, how many puffs of short-acting bronchodilator (e.g., Ventolin or Proventil) have you used each day?

- ☐ 0 None
- ☐ 1 1 - 2 puffs most days
- ☐ 2 3 - 4 puffs most days
- ☐ 3 5 - 8 puffs most days
- ☐ 4 9 - 12 puffs most days
- ☐ 5 13 - 16 puffs most days
- ☐ 6 More than 16 puffs most days

Figure S2. Page 2 of PAX Feasibility mini-Asthma Control Questionnaire (mini-ACQ).

Asthma Clinical Research Network

WISCONSIN UPPER RESPIRATORY SYMPTOM SURVEY - 21

Subject ID: ___ ___ - ___ ___ - ___ ___ ___

Subject Initials: ___ ___ ___

Return Visit Number: ___ ___ ___

Return Visit Date: ___ ___ / ___ ___ / ___ ___ (Month / Day / Year)

Today's date ___ ___ / ___ ___ / ___ ___ ___ ___ (Month / Day / Year) (ddate)

Please fill in one box for each of the following items:

		Not sick	Very Mildly		Mildly		Moderately		Severely	
1.	How sick do you feel **today**?	❑0	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1000)

Please rate the **average severity of your cold symptoms over the last 24 hours** for each symptom:

		Do not have this symptom	Very Mild		Mild		Moderate		Severe	
2.	Runny nose	❑0	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1010)
3.	Plugged nose	❑0	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1020)
4.	Sneezing	❑0	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1030)
5.	Sore throat	❑0	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1040)
6.	Scratchy throat	❑0	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1050)
7.	Cough	❑0	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1060)
8.	Hoarseness	❑0	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1070)
9.	Head congestion	❑0	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1080)
10.	Chest congestion	❑0	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1090)
11.	Feeling tired	❑0	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1100)

Over the last 24 hours, how much has your cold interfered with your ability to:

		Not at all	Very Mildly		Mildly		Moderately		Severely	
12.	Think clearly	❑0	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1110)
13.	Sleep well	❑0	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1120)
14.	Breathe easily	❑0	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1130)
15.	Walk, climb stairs, exercise	❑0	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1130)
16.	Accomplish daily activities	❑0	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1140)
17.	Work outside the home	❑0	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1150)
18.	Work inside the home	❑0	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1160)
19.	Interact with others	❑0	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1170)
20.	Live your personal life	❑0	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1180)

Compared to yesterday, I feel that my cold is...

	Very much better	Somewhat better	A little better	The same	A little worse	Somewhat worse	Very much worse	
21.	❑1	❑2	❑3	❑4	❑5	❑6	❑7	(1190)

WURSS - 21 (Wisconsin Upper Respiratory Symptom Survey) 2004
Created by Bruce Barrett MD PhD et al., UW Department of Family Medicine, 777 S. Mills St. Madison, WI 53715, USA
07/22/2005 version 1.0

WURSS-21

Supplement Figure S3. WURSS-21 Survey form used in PAX study.

Asthma Clinical Research Network
NIH/NHLBI

PAX COLD QUESTIONNAIRE

Subject ID: ___ ___ - ___ ___ - ___ ___ ___

Subject Initials: ___ ___ ___

Contact Date: ___ ___ / ___ ___ / ___ ___
Month Day Year

1. How many colds do you get every year? ___ ___ colds per year

2. How severe are your colds usually?
   - ☐ Extremely severe
   - ☐ Very severe
   - ☐ Severe
   - ☐ Moderate
   - ☐ Mild
   - ☐ Extremely mild (trivial)

3. When you get colds, how often do they make your asthma worse?
   → *If Never, STOP HERE.*
   - ☐ Always
   - ☐ Usually
   - ☐ Sometimes
   - ☐ Rarely
   - ☐ Never

4. When colds make your asthma worse, how severe does your asthma usually get?
   - ☐ Extremely severe
   - ☐ Very severe
   - ☐ Severe
   - ☐ Moderate
   - ☐ Mild
   - ☐ Extremely mild (trivial)

Supplement Figure S4. PAX Cold Questionnaire used in PAX study.