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Prediction of respiratory outcome in extremely low gestational age infants

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Abstract

Background—Bronchopulmonary dysplasia (BPD) is a commonly used outcome for randomized neonatal trials.

Objectives—To determine whether a diagnosis of BPD or respiratory morbidity (RM_1 or RM_2) at 12 months corrected age better predicted subsequent respiratory morbidity in extremely low gestational age infants (23–28 weeks of gestation).

Methods—Initial analysis was undertaken in a development cohort of 76 infants who underwent pulmonary function tests (PFTs) at 12 months corrected age. Parents completed infant respiratory diaries two weeks pre PFTs. Analysis was then undertaken in a validation cohort of 227 infants whose parents completed a four week respiratory diary when their infant was 12 months corrected age. BPD at 28 days (BPD_{28d}) and 36 weeks post menstrual age (BPD_{36w}), RM_1 (≥ three days and/or nights of cough, wheeze, and/or medicine use) and RM_2 (≥ four days and/or nights of

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cough, wheeze and/or respiratory medicine use) each week for two weeks at 12 months corrected age were assessed with regard to prediction of respiratory outcomes at 24 months documented by respiratory health questionnaires.

Results—BPD_{28d} and BPD_{36w} were not significantly associated with any respiratory outcome. Areas under the receiver operator curves were significantly better for either definition of RM than BPD_{28d} or BPD_{36w} for all outcomes.

Conclusions—Respiratory morbidity documented by parental completed diaries at 12 months corrected age better predicted respiratory outcome at 24 months corrected age than BPD regardless of diagnostic criteria.

Keywords

bronchopulmonary dysplasia; pulmonary function; premature infant; respiratory outcome

INTRODUCTION

Infants born at extremely low gestational ages frequently develop bronchopulmonary dysplasia (BPD) and chronic respiratory morbidity [1]. Chronic respiratory morbidity is important as it increases healthcare utilization and the related healthcare costs, as well as adversely impacting on the lives of affected children and their families. Hence, it is essential to determine how chronic respiratory morbidity is best predicted and hence appropriate interventions be most effectively targeted. The incidence of survival without BPD is a commonly used primary outcome in clinical trials, although a diagnosis of BPD may, however, correlate poorly with respiratory morbidity in the first years after birth. For example, Tyson and colleagues studied 807 infants randomised to placebo or Vitamin A and found a small, but significant reduction in the incidence of BPD in infants receiving Vitamin A [2]. Yet, a follow-up study when the infants were one year corrected age revealed no benefits in longer term pulmonary outcome [3]. In contrast, in a randomised trial, recombinant human superoxide dismutase (rhSOD) was not associated with a reduction in the combined outcome of death or BPD at 36 weeks post-menstrual age (PMA). A follow-up study, however, demonstrated significant reductions in episodes of respiratory illness severe enough to require the use of respiratory medications at 12 months corrected age and reductions in hospital admissions and emergency room visits in the highest risk infants who received rhSOD [4].

Parent completed diary cards, to assess respiratory status and respiratory morbidity at follow up have been developed for prematurely born infants [5, 6]. The aim of this study was to determine whether respiratory morbidity as recorded by parental completed diary cards at one year corrected was a better predictor of subsequent respiratory morbidity at follow up, that is at two years of age, than a diagnosis of BPD, whether defined as oxygen dependency at 28 days after birth (BPD_{28d}) or 36 weeks PMA (BPD_{36w}).

METHODS

Study population

The subjects were part of the United Kingdom Oscillation Study (UKOS) [7]. Infants born between 23 and 28 weeks gestational age entered into UKOS were randomised to high frequency oscillation or conventional mechanical ventilation within one hour of birth. There were no statistically significant differences between the two groups in short-term pulmonary outcomes, pulmonary function results at one year [8] or respiratory morbidity up to 24 months corrected age [9], hence the results were pooled for this study. The South Thames Multicentre Research Ethics Committee and the local research-ethics committee at each participating centre approved the studies.

Initial analysis in this study was undertaken in a development cohort who were a subset of 76 infants who participated in detailed pulmonary function assessments at 12 months corrected age (pulmonary function subset) [8]. Subsequent analysis was undertaken in a validation cohort of 227 UKOS infants whose parents completed a four week diary card when their infant was 12 months corrected age (Figure 1).

Diary card and respiratory questionnaire

Prior to the PFTs, parents were asked to complete a two week infant respiratory diary card to assess whether or not their infant was too symptomatic to undergo sedation for pulmonary function testing. Parents recorded daily (both day and night) whether their child had coughed, wheezed and/or had taken respiratory medication (inhaled bronchodilators and/or inhaled/systemic corticosteroids).

Paediatricians completed a respiratory questionnaire with parents when their infant was 24 months corrected age during routine follow-up visits. The questionnaires recorded parental reports of whether the child had suffered from cough or wheeze, taken any medication to control or prevent respiratory symptoms or had been admitted to the hospital for respiratory illnesses (all were analysed as yes/no).

Analysis

The definition of respiratory morbidity (RM_1) was determined *a priori* as being at least three days per week of the child having cough, wheeze, and/or use of respiratory medicines (all recorded as yes/no), each week during the two week pre-PFT period (RM_1). This definition was chosen as it was felt likely to reflect on going respiratory morbidity rather than short lasting symptoms associated with an acute respiratory tract infection. A sensitivity analysis was then performed using at least four days and/or nights of cough, wheeze, and/or use of respiratory medicines each week for the two week pre PFT period (RM_2). For the initial analysis data from the two-week diary was used (n=62 were completed).

The association of BPD_{28d} and BPD_{36w} with the respiratory outcomes at 24 months corrected age were examined. The area under the ROC curve was calculated to compare the strength of association between variables. The associations between respiratory outcomes and RM_1 and RM_2 were then examined. The strength of associations of BPD_{28}, BPD_{36} and

RM_1 and RM_2 with respiratory outcomes at 24 months corrected age were compared using the test of equality of ROC areas [10].

A further validation cohort of thirty-four infants who underwent pulmonary function testing and whose parents completed four week diary cards were used to validate the definitions of RM_1 and RM_2. The sensitivity and specificity, positive and negative predictive values of RM_1 and $RM_2$for respiratory outcomes at 24 months corrected age were then calculated using the prior definition and the sensitivity definition described above. A further sensitivity analysis was performed to assess the predictive ability of RM_1 and RM_2 but using the 227 UKOS infants whose parents completed the four week diary cards at 12 months corrected age. All analyses were performed using Stata v12.1.

RESULTS

Eighty-four percent of the 76 infants in the development cohort were oxygen dependent at 28 days after birth (BPD_{28d}) and 59% were oxygen dependent at 36 weeks PMA (BPD_{36w}) (Table 1). The demographics of the 227 infants in the validation cohort whose results were included in the subsequent analysis were similar (Table 1).

In the development cohort, neither BPD_{28d} nor BPD_{36w} were significantly related to any respiratory outcome (Table 2). In the validation cohort whose parents completed the four week diary cards, there was no evidence that either definition of BPD was related to any of the respiratory outcomes at 24 months corrected age (Table 2). All respiratory outcomes at 24 months corrected age (except hospital admissions) were significantly related to both RM_1 and RM_2 (Table 3).

The areas under the ROC curves were higher for all respiratory outcomes using either RM_1 and RM_2 as compared to either BPD_{28d} or BPD_{36w} (Table 4). RM_1 and RM_2 compared to either BPD_{28d} or BPD_{36w} were statistically significantly more predictive of later outcomes, as judged by comparing the ROC curves, for the combined outcome of cough, wheeze and/or use of respiratory medicines for RM_1 compared to BPD_{28d} and for cough for RM_1 compared to BPD_{36w} (Table 4). Similar patterns were observed for RM_2. In the sensitivity analysis using the larger cohort (n=227), all respiratory outcomes at 24 months were better predicted by RM_1 and RM_2 than BPD_{28d} and BPD_{36w}.

Analysis of the four week diary card data demonstrated that RM_1 and RM_2 significantly predicted cough, wheeze and/or use of respiratory medications documented by the 24 month corrected age questionnaire (Table 5).

RM_1 and RM_2 had specificities ranging 58% to 91% and sensitivity ranging from 64% to 81% for the different follow-up respiratory outcomes at 24 months corrected age in the development cohort. Positive and negative predictive values ranged from 42% to 86% and 67% to 85% respectively. In the validation cohort, the sensitivities and specificities were similar but with narrower confidence intervals (Table 6).

DISCUSSION

We have demonstrated that respiratory morbidity (RM_1 and RM_2) as derived from parent completed diary cards completed at one year corrected age was a better predictor of excess respiratory problems at 24 months corrected age than a diagnosis of BPD in extremely low gestational age infants. We undertook the initial analysis on a small subset of 'UKOS' infants as we had very detailed information about them including a two week diary card prior to pulmonary function testing (development cohort). Our subsequent analysis, on a larger subset whose parents also completed four week diary cards at 12 months corrected age (validation cohort), regardless of which BPD definition was used, demonstrated that RM was a significantly better predictor of respiratory outcomes at 24 months corrected age.

We compared RM_1 and RM_2 to two definitions of BPD. Studies have defined BPD as an oxygen requirement at 28 days after birth or 36 weeks PMA. Shennan and colleagues suggested that the need for oxygen supplementation at 36 weeks PMA, rather than 28 days after birth, was a more accurate predictor of longer term outcome [11]. The definition, however, did not correlate well specifically with long term pulmonary outcome [11], whereas we had found in a subsequent study that the 28 day definition to be a better predictor of long term pulmonary outcome [12]. At an NIH consensus conference, the diagnosis of BPD was agreed to be made at 28 days and also included assignment of severity of BPD at 36 weeks PMA in prematurely born infants [13]. Nevertheless, when a cohort of premature infants was followed to 18 to 22 months corrected age, the NIH definition of BPD correctly predicted long-term respiratory morbidity only 35–40% of the time, although the accuracy increased as the severity of BPD worsened [14]. A further major limitation in using BPD as an outcome is that premature infants who do not develop BPD can also suffer chronic respiratory problems.

The definitions of RM_1 and RM_2 were based on the results of a two week diary card, but we validated the analysis using results from a four week diary in a larger dataset. In that analysis, the infant was required to be symptomatic in any two weeks of a four week period (not necessarily consecutive weeks). We again demonstrated that RM_1 and RM_2 were significant predictors of respiratory outcomes documented at 24 months corrected age. These results highlight that symptoms of cough and/or wheeze and requirement for respiratory medications are predictive of longer term abnormal respiratory outcome.

We decided *a priori* to assess a definition of RM as cough, wheeze and/or medication use on three or more days each week for a two week consecutive period. That definition was predictive, but our sensitivity analysis demonstrated that RM_2 (at least four days of cough/wheeze/medication use per week for a two week consecutive period) tended to be a stronger predictor of respiratory outcome at 24 months corrected age. Those results suggest, not surprisingly, the more symptomatic the infant is the more likely they will suffer an abnormal respiratory outcome. We did not, however, test this hypothesis further, as using a definition which involved even more days of cough/wheeze/medicine use, although likely to be more specific, would lose sensitivity.

Our study has some potential limitations. The data were prospectively collected to assess respiratory outcome in a high risk population, but were retrospectively analysed. The infants had been entered into a randomised trial (UKOS) [7], but there were no significant differences in the short term outcomes between the two groups, hence we pooled the data for the analysis. Data from only 76 infants (development cohort) were included in the initial analysis as they had had PFTs at 12 months corrected age, but they were representative of the entire UKOS population with regard to their demographics [8]. Hence, we feel these results are generalisable to larger populations of extremely low gestational age infants. At 24 months corrected age, parents completed respiratory questionnaires with their paediatrician who had the hospital records with them so we feel the questionnaires reflected the respiratory outcomes of the infants. Indeed, comparison has shown a good correlation of parental reports with paediatrician records for hospital admissions, asthma and bronchitis [15]. We undertook a subsequent analysis on a larger cohort of infants (validation cohort) and the results confirmed that RM_1 and RM_2 compared to BPD_{28} and BPD_{36} were better predictors of respiratory outcome at 24 months corrected age.

In conclusion, we have demonstrated that respiratory morbidity diagnosed from a two week parent completed diary at one year corrected age better predicted abnormal respiratory outcomes at 24 months corrected age than BPD defined either as oxygen dependency at 28 days or 36 weeks PMA. We, therefore, suggest that data from parent completed diary cards at one year corrected age rather than BPD, may be a better outcome measure when assessing the efficacy of interventions aimed at improving long term respiratory outcome in extremely low gestational age infants.

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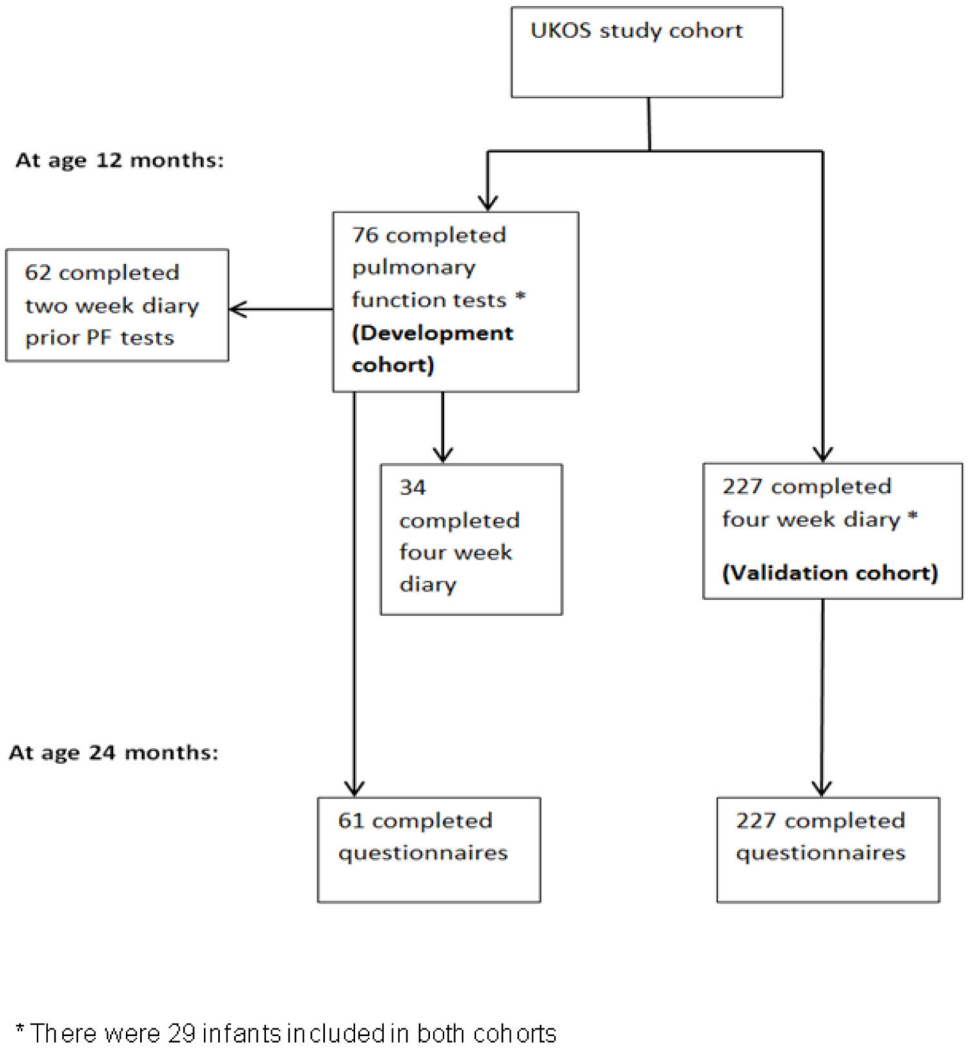

Figure 1.
Flow diagram of the cohorts

Table 1

Demographics of the infants who underwent pulmonary function testing (development cohort) and of infants whose parents completed the four week diary card (validation cohort)

The data are presented as median (range) or n (%)		
	Development cohort	**Validation cohort**
N	**76**	**227**
Male	42 (55%)	113 (50%)
Gestational age (week)	26 [23 to 28]	27 [23 to 28]
Birth weight (g)	870 [458 to 1335]	890 [500 to 1459]
Birth weight z-score	−0.47 [−3.45 to 1.73]	−0.46 [−3.30 to 2.41]
Small for gestational age (birth weight z-score <−1.28)	13 (17%)	53 (23%)
Multiple birth	16 (21%)	59 (26%)
Race		
White	56 (74%)	208 (92%)
black	13 (17%)	8 (4%)
Other	7 (9%)	11 (5%)
Maternal smoking in pregnancy	13 (20%)	46 (20%)
Oxygen dependent at 28 days	64 (84%)	190 (84%)
Oxygen dependent at 36 wk PMA	45 (59%)	142 (63%)
Oxygen dependent at discharge	14 (18%)	50 (22%)
Days on ventilator support	14 [0 to 112]	8 [0 to 62]
Air leak	11 (14%)	28 (12%)

Table 2

Association of BPD defined as either oxygen dependency at 28 days or at 36 weeks PMA with respiratory outcomes

(a) Analysis using the data from the development cohort (n=76)				
i) Oxygen dependency at 28 days (BPD_{28d})				
Respiratory outcome at 24 months corrected age		**OR (95% CI)**	**P-value**	**Area under ROC curve**
Respiratory hospital admission	61	3.89 (0.45, 33.6)	0.22	0.55
Cough	60	2.66 (0.50, 14.1)	0.25	0.56
Wheeze	61	1.85 (0.35, 9.86)	0.47	0.54
Respiratory medications (all types)	60	1.52 (0.37, 6.33)	0.56	0.53
Any cough, wheeze and/or use of respiratory medications	61	1.58 (0.38, 6.55)	0.53	0.53
ii) Oxygen dependency at 36 wk PMA (BPD_{36w})				
Respiratory outcome at 24 months corrected age		**OR (95% CI)**	**P-value**	**Area under ROC curve**
Respiratory hospital admission	61	1.58 (0.50, 5.00)	0.43	0.55
Cough	60	2.43 (0.81, 7.27)	0.11	0.60
Wheeze	61	2.02 (0.65, 6.28)	0.23	0.58
Respiratory Medications (all types)	60	3.41 (1.16, 9.98)	0.025	0.65
Any cough, wheeze and/or use of respiratory medications	61	2.65 (0.93, 7.58)	0.069	0.62

(b) Analysis using data from the validation cohort with four week diary card results (n=227)				
i) Oxygen dependency at 28 days (BPD_{28d})				
Respiratory outcome at 24 months corrected age	**N**	**OR (95% CI)**	**P-value**	**Area under ROC curve**
Respiratory hospital admission	225	0.94 (0.38, 2.32)	0.90	0.50
Cough	226	1.22 (0.60, 2.48)	0.59	0.51
Wheeze	217	1.72 (0.80, 3.71)	0.17	0.54
Respiratory medications (all types)	227	1.97 (0.97, 4.01)	0.062	0.55
Any cough, wheeze and/or use of respiratory medications	227	1.56 (0.77, 3.18)	0.22	0.53
ii) Oxygen dependency at 36 wk PMA (BPD_{36w})				
Respiratory outcome at 24 months corrected age	**N**	**OR (95% CI)**	**P-value**	**Area under ROC curve**
Respiratory hospital admission	225	1.41 (0.69, 2.90)	0.35	0.54
Cough	226	1.10 (0.64, 1.88)	0.73	0.51
Wheeze	217	0.90 (0.51, 1.56)	0.70	0.51
Respiratory Medications (all types)	227	1.55 (0.90, 2.66)	0.12	0.55

(b) Analysis using data from the validation cohort with four week diary card results (n=227)

i) Oxygen dependency at 28 days (BPD_{28d})

Respiratory outcome at 24 months corrected age	N	OR (95% CI)	P-value	Area under ROC curve
Any cough, wheeze and/or use of respiratory medications	227	1.33 (0.76, 2.31)	0.31	0.53

* Difference is BPD versus no BPD

** P-value from t-test

Table 3

Association of RM_1 and RM_2 with PFT results and respiratory outcomes at 24 months corrected age

(a) Analysis using data from the development cohort (n=76)

		RM_1			RM_2		
Respiratory outcome at 24 months corrected age		**OR (95% CI)**	**P-value**	**Area under ROC curve**	**OR (95% CI)**	**P-value**	**Area under ROC curve**
Respiratory hospital admission	52	3.08 (0.88, 10.7)	0.077	0.64	5.72 (1.58, 20.7)	0.008	0.70
Cough	51	11.7 (3.01, 45.4)	< 0.001	0.77	12.5 (3.25, 48.1)	< 0.001	0.77
Wheeze	52	5.5 (1.48, 20.5)	0.011	0.70	4.58 (1.33, 15.8)	0.016	0.68
Respiratory medications (all types)	51	7.08 (2.05, 24.5)	0.002	0.73	12.0 (2.85, 50.6)	0.001	0.76
Any cough, wheeze and/or use of respiratory medications	52	9.45 (2.62, 34.1)	0.001	0.75	20.0 (3.87, 102.9)	< 0.001	0.78

(b) Analysis using data from the validation cohort with results from the four week diary card (n=227)

		RM_1			RM_2		
Respiratory outcome at 24 months corrected age	**N**	**OR (95% CI)**	**P-value**	**Area under ROC curve**	**OR (95% CI)**	**P-value**	**Area under ROC curve**
Respiratory hospital admission	225	5.05 (2.34, 10.9)	< 0.001	0.69	3.90 (1.92, 7.95)	< 0.001	0.66
Cough	226	5.14 (2.91, 9.06)	< 0.001	0.69	5.54 (3.09, 9.91)	< 0.001	0.69
Wheeze	217	5.16 (2.87, 9.28)	< 0.001	0.69	5.82 (3.21, 10.6)	< 0.001	0.70
Respiratory medications (all types)	227	8.02 (4.32, 14.9)	< 0.001	0.73	10.0 (5.06, 19.8)	< 0.001	0.74
Any cough, wheeze and/or use of respiratory medications	227	7.00 (3.69, 13.3)	< 0.001	0.72	9.95 (4.75, 20.8)	< 0.001	0.73

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Table 4

Comparison of ROC areas of RM_1, RM_2, BPD_{28d} and BPD_{36w} with respiratory outcomes at 24 months corrected age

(a) Analysis using data from the development cohort (n=76)

Respiratory outcome at 24 months	N	Area under ROC curve				
		RM_1	BPD_{28d} *	P-value	BPD_{36w} *	P-value
Respiratory hospital admission	52	0.64	0.55	0.33	0.52	0.26
Cough	51	0.77	0.54	0.0008	0.57	0.027
Wheeze	52	0.70	0.51	0.015	0.54	0.086
Respiratory medications (all types)	51	0.73	0.49	0.0017	0.60	0.18
Any cough, wheeze and/or use of respiratory medications	52	0.75	0.50	0.0004	0.57	0.042

Respiratory outcome at 24 months	N	Area under ROC curve				
		RM_2	BPD_{28d} *	P-value	BPD_{36w} *	P-value
Respiratory hospital admission	52	0.70	0.55	0.067	0.52	0.065
Cough	51	0.77	0.54	0.0008	0.57	0.030
Wheeze	52	0.68	0.51	0.036	0.54	0.16
Respiratory medications (all types)	51	0.76	0.49	0.0001	0.60	0.084
Any cough, wheeze and/or use of respiratory medications	52	0.78	0.50	<0.001	0.57	0.012

(b) Analysis using data from the validation cohort with four week diary card results (n=227)

Respiratory outcome at 24 months	N	Area under ROC curve				
		RM_1	BPD_{28d}	P-value	BPD_{36w}	P-value
Respiratory hospital admission	225	0.69	0.50	< 0.001	0.54	0.003
Cough	226	0.69	0.51	< 0.001	0.51	< 0.001
Wheeze	217	0.69	0.54	< 0.001	0.51	< 0.001
Respiratory medications (all types)	227	0.73	0.55	< 0.001	0.55	< 0.001
Any cough, wheeze and/or use of respiratory medications	227	0.72	0.53	< 0.001	0.53	< 0.001

Respiratory outcome at 24 months	N	Area under ROC curve				
		RM_2	BPD_{28d}	P-value	BPD_{36w}	P-value
Respiratory hospital admission	225	0.66	0.50	0.0003	0.54	0.017
Cough	226	0.69	0.51	< 0.001	0.51	< 0.001
Wheeze	217	0.70	0.54	< 0.001	0.51	< 0.001

(b) Analysis using data from the validation cohort with four week diary card results (n=227)

Respiratory outcome at 24 months	N	Area under ROC curve				
		RM_1	BPD_{28d}	P-value	BPD_{36w}	P-value
Respiratory medications (all types)	227	0.74	0.55	< 0.001	0.55	< 0.001
Any cough, wheeze and/or use of respiratory medications	227	0.73	0.53	< 0.001	0.53	< 0.001

* Note these values are different from Table 2 since the group of children included in this analysis is smaller

Table 5

Validation of RM_1 and RM_2 data using the four week diary card data from the development cohort

		RM_1			RM_2		
Respiratory outcome at 24 months corrected age	**N**	**OR (95% CI)**	**P-value**	**Area under ROC curve**	**OR (95% CI)**	**P-value**	**Area under ROC curve**
Respiratory hospital admission	29	6.50 (1.05, 40.1)	0.044	0.71	4.67 (0.87, 25.1)	0.073	0.68
Cough	29	16.3 (1.63, 163)	0.017	0.79	9.00 (1.35, 59.8)	0.023	0.75
Wheeze	29	8.67 (1.39, 53.8)	0.020	0.74	6.50 (1.20, 35.6)	0.03	0.72
Respiratory medications (all types)	29	16.3 (2.46, 107)	0.004	0.80	14.0 (2.30, 85.2)	0.004	0.79
Any cough, wheeze and/or use of respiratory medications	29	16.3 (2.46, 107)	0.004	0.80	14.0 (2.30, 85.2)	0.004	0.79

Table 6

Sensitivity, specificity, positive predictive value and negative predictive value for the RM_1 and $RM_2$and the respiratory outcome at 24 months

(a) Analysis using data from the development cohort (n=76)

	RM_1				RM_2			
Respiratory outcome at 24 months	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Positive Predictive Value (95% CI)**	**Negative Predictive Value (95%CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Positive Predictive Value (95% CI)**	**Negative Predictive Value (95% CI)**
Respiratory hospital admission	69% (41, 89%)	58% (41, 75%)	42% (23, 63%)	81% (61, 93%)	69% (41, 89%)	72% (55, 86%)	52% (30, 74%)	84% (66, 95%)
Cough	81% (58, 95%)	73% (54, 88%)	68% (47, 85%)	85% (65, 96%)	71% (48, 89%)	83% (65, 94%)	75% (51, 91%)	81% (63, 93%)
Wheeze	77% (50, 93%)	63% (45, 79%)	50% (30, 70%)	85% (65, 96%)	65% (38, 86%)	71% (54, 85%)	52% (30, 74%)	81% (63, 93%)
Respiratory medications (all types)	71% (51, 87%)	74% (52, 90%)	77% (56, 91%)	68% (47, 85%)	64% (44, 81%)	87% (66, 97%)	86% (64, 97%)	67% (47, 83%)
Any cough, wheeze and/or use of respiratory medications	72% (53, 87%)	78% (56, 93%)	81% (61, 93%)	69% (48, 86%)	66% (46, 82%)	91% (72, 99%)	91% (70, 99%)	68% (49, 83%)

(b) Analysis using data from the validation cohort with results from the four week diary card (n=227)

	RM_1				RM_2			
Respiratory outcome at 24 months	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Positive Predictive Value (95% CI)**	**Negative Predictive Value (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Positive Predictive Value (95% CI)**	**Negative Predictive Value (95% CI)**
Respiratory hospital admission	76% (61, 88%)	61% (54, 68%)	31% (22, 41%)	92% (85, 96%)	67% (51, 80%)	66% (59, 73%)	31% (22, 42%)	90% (83, 94%)
Cough	66% (57, 75%)	72% (63, 80%)	68% (58, 77%)	71% (62, 78%)	61% (51, 70%)	78% (70, 85%)	71% (61, 80%)	69% (60, 77%)
Wheeze	69% (58, 78%)	70% (62, 78%)	62% (51, 71%)	76% (68, 84%)	64% (53, 74%)	77% (68, 84%)	66% (55, 75%)	75% (67, 83%)
Respiratory medications (all types)	66% (57, 74%)	80% (71, 88%)	82% (73, 89%)	64% (55, 72%)	61% (52, 69%)	87% (78, 93%)	86% (77, 92%)	62% (54, 70%)
Any cough, wheeze and/or use of respiratory medications	62% (54, 70%)	81% (71, 89%)	85% (76, 91%)	56% (47, 65%)	57% (49, 66%)	88% (79, 94%)	89% (81, 95%)	55% (46, 63%)